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(54) Pharmaceutical compositions for the treatment of ischemic brain damage

(57) The use of a compound which has Na^+/H^+ exchange system inhibition activity, in particular a substituted guanidine derivative, or a pharmaceutically acceptable acid addition salt thereof, in the manufacture of a pharmaceutical composition for the treatment of ischemic brain damage such as cerebral infarction, cerebral embolism and cerebral thrombus.

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Description

[0001] The present invention relates to a pharmaceutical composition for the treatment of ischemic brain damage. More particularly, the invention relates to a pharmaceutical composition comprising as an active ingredient a specific guanidine derivative having a Na^+/H^+ exchange system inhibition activity, which is particularly useful for the prevention of death at the acute phase and sequelae following ischemia, brain edema, cerebral microcirculatory disorder and for neuroprotective purpose.

[0002] The mortality rate from cerebrovascular disorders has been decreasing in these years but is still very high. Even now the number of patients with ischemic sequela or who receive treatment in hospital or attend a hospital is increasing. When ischemia in the brain continues for a certain time of period, various irreversible changes occur to cause necrosis in the brain tissue, namely, cerebral infarction, which induces various neural symptoms. Appropriate treatments during the acute phase will contribute to reduction in the mortality rate at the initial phase and to alleviation of sequelae.

[0003] Na^+/H^+ exchangers are plasma membrane proteins, which release H^+ ion outside cells concomitant with uptake of Na^+ ion into cells. Since the migration of Na^+ ion is known to be accompanied by water transfer, it is considered that Na^+/H^+ exchangers will regulate intracellular pH level and a cell volume. There is evidence to suggest that the Na^+/H^+ exchangers will be activated by ischemia and reperfusion in the tissue to increase the level of Na^+ ion in the cells and in turn Ca^{2+} ion via Na^+/Ca^{2+} exchangers, which eventually cause various cytotoxic states.

[0004] It is reported that the infarcted area in the heart caused by ischemia and reperfusion was reduced in ischemia model animals by inhibiting Na^+/H^+ exchangers. As far as ischemic brain damage is concerned, no report is made on any animal experiments. It is reported on a cellular level that amiloride attenuated cell swelling induced by acid loading on the cultured glial cells (Kempski, O., et al., Stroke, 19, 385-392, 1988). However, this report does not explain any correlation between brain edema and Na^+/H^+ exchange inhibitors, because amiloride has many other actions due to its low specificity, although it has a Na^+/H^+ exchange inhibition action. Rather, amiloride is used as an Na^+/Ca^{2+} exchange inhibitor in some papers. Thus, the causal relation is unclear if the cell swelling was prevented by inhibiting the Na^+/H^+ exchange system.

[0005] Another reason to deny the reasoning that the results obtained with the cultured glial cells will explain the relationship between brain edema and Na^+/H^+ exchangers, is the fact that cell swelling was prevented by acetazolamide in the reported experiments. Acetazolamide is known as a diuretic agent. In fact, no significant effect of preventing cerebral edema was noted with ischemic animal models in vivo (Goto et al., NO-SOTCHU JIKKEN HANDBOOK (Experimental Handbook of Ischemic Insult), chapter 7, "Vascular permeability and brain edema", pages 629-733, published by IPC Co., Ltd.; Neurosurgery, 6, 149-154, 1980; Stroke, 2, 456-460, 1971). Reasonable reading of these reports indicates that the experimental data obtained with the cultured glial cells cannot be used as reflecting on the prevention of brain edema in vivo.

[0006] Compounds having a Na^+/H^+ exchange inhibitory activity are mentioned in, e.g., Japanese Patent KOKAI (Laid-Open) No. 9-67340, for use in the prevention or treatment of cerebral infarction. However, no pharmacological data was presented to support the alleged use. Indeed, there was no report to suggest that the Na^+/H^+ exchange inhibitory activity in association with the prevention of ischemic cerebrovascular disorders in vivo.

[0007] Main drugs currently employed for the clinical treatment of cerebral apoplexy in the acute phase are compounds like glycerol, which are considered to act through a mechanism to diminish edema by their high permeability or to prevent the blood coagulation mechanism. However, those drugs are not satisfactorily effective. A more serious problem is that anti-blood coagulants contraindicate hemorrhagic conditions or cerebral embolism. Thus, pre-tests for diagnosis become necessary, which disadvantageously retards the onset of immediate treatment required for the acute phase of ischemia. It is therefore desired to provide a drug effectively applicable to the acute phase of any conditions without requiring pre-test for diagnosis.

[0008] The present inventors have made extensive studies to develop compounds effective for the prevention of ischemic brain damage. As a result it has been found that compounds having a Na^+/H^+ exchange inhibitory activity exhibit an excellent effect of improving cerebral infarction and cerebral edema. Therefore the present invention has been attained. In view of the report as stated hereinabove on the experiments using the cultured glial cells in vitro, candidate compounds was elucidated in vivo in the present invention to find compounds effective for ischemic edema and infarction. It is quite likely that the Na^+/H^+ exchange system inhibitors will be drugs effective for the treatment of ischemic cerebrovascular disorders, especially in the acute phase, and available for the type of brain damage concomitant with hemorrhage, since Na^+/H^+ exchangers do not significantly affect either the blood coagulation cycle or the fibrinolytic system.

[0009] Accordingly, the present invention thus provides a pharmaceutical composition for the treatment of ischemic brain damage comprising as an active ingredient a compound having the Na^+/H^+ exchange system inhibition activity or a salt thereof, together with a pharmaceutically acceptable carrier.

[0010] In the preferred embodiment, said ischemic brain damage is cerebral infarction, cerebral embolism, or cerebral

thrombus.

[0011] Further, the present invention provides a method for treating ischemic brain damage, which comprises administering into a patient a compound having a Na^+/H^+ exchange system inhibition activity or a salt thereof in a pharmacologically effective amount.

[0012] Further, the present invention provides use of a compound having a Na^+/H^+ exchange system inhibition activity in the manufacture of a pharmaceutical composition for the treatment of ischemic brain damage.

Fig. 1 is a graph showing the percentage of infarcted area observed in the vehicle group and the group treated with Compound 1, which was induced in rats with transient ischemia in Example 1.

Fig. 2 is a graph showing the percentage of infarcted area observed in the vehicle group and the group treated with Compound 2, which was induced in rats with transient ischemia in Example 2.

Fig. 3 is a graph showing the percentage of infarcted area observed in the vehicle group and the group treated with Compound 3, which was induced in rats with transient ischemia in Example 3.

Fig. 4 is a graph showing the brain water content in rats with transient brain ischemia, observed in the normal control group, the vehicle group and the groups treated with 0.3 mg/kg and 1 mg/kg of Compound 1 in Example 4.

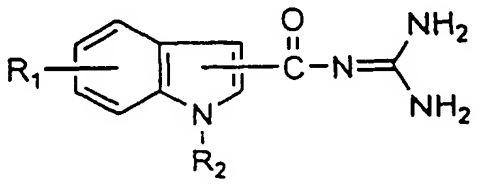
Fig. 5 is a graph showing the brain water content in rats with transient brain ischemia, observed in the normal control group, the vehicle group and the groups treated with 3 mg/kg of Compound 2 in Example 5.

Fig. 6 is a graph showing the brain water content in rats with transient brain ischemia, observed in the normal control group, the vehicle group and the groups treated with 0.3 mg/kg and 1 mg/kg of Compound 3 in Example 6.

[0013] The compounds used in the present invention as the Na^+/H^+ exchange system inhibitors are described below in detail.

[0014] As the Na^+/H^+ exchange system inhibitors or salts thereof used in the pharmaceutical compositions according to the present invention, any compounds may be used without particular restriction, so long as these compounds have an activity of inhibiting the Na^+/H^+ exchange system. The invention includes the following embodiments.

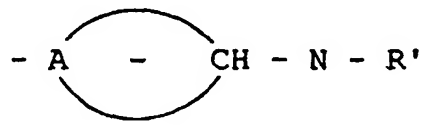
(a) The present invention relates to a pharmaceutical composition comprising an indoloylguanidine derivative described in Japanese Patent KOKAI (Laid-Open) No. 8-208602, which is represented by the following general formula (1):



(1)

wherein:

R_1 represents one or more, the same or different, substituent(s) which is selected from the group consisting of a hydrogen atom, a C_1-C_8 alkyl group, a substituted C_1-C_8 alkyl group, a C_2-C_6 alkenyl group, a C_2-C_6 alkynyl group, a C_3-C_7 cycloalkyl group, a halogen atom, nitro, a C_2-C_8 alkanoyl group, an arylalkanoyl group having carbon atoms up to 10, an aroyl group having carbon atoms up to 11, carboxyl, a C_2-C_6 alkoxycarbonyl group, an aromatic group, a group shown by formula: $-OR_3$, $-NR_6R_7$, $-SO_2NR_6R_7$ or $-S(O)_nR_{40}$, and a group shown by formula:



wherein A represents an oxygen atom or a group shown by formula: $-S(O)_n-$ or $-N(R_{50})-$ wherein R_{50} is a hydrogen atom or a C_1-C_8 alkyl group, R' represents a hydrogen atom, a C_1-C_8 alkyl group or a substituted C_1-C_8 alkyl group; and the ring represents a saturated 3 to 8-membered hetero ring containing one nitrogen atom;

R_2 represents a hydrogen atom, a C_1-C_8 alkyl group, a substituted C_1-C_8 alkyl group, a C_3-C_7 cycloalkyl group, hydroxy, a C_1-C_6 alkoxy group, an aromatic group or a group shown by formula: $-CH_2R_{20}$;

R_3 represents a hydrogen atom, a C_1-C_8 alkyl group, a substituted C_1-C_8 alkyl group, a C_3-C_7 cycloalkyl group, an aromatic group or a group shown by formula: $-CH_2R_{30}$, in which R_{30} represents an C_2-C_6 alkenyl group or an C_2-C_6 alkynyl group;

each of R_6 and R_7 independently represents a hydrogen atom, a C_1-C_8 alkyl group, a substituted C_1-C_8 alkyl group, a C_3-C_7 cycloalkyl group, a C_2-C_8 alkanoyl group, an arylalkanoyl group having carbon atoms up to 10, an aroyl group having carbon atoms up to 11, an aromatic group or a group shown by formula: $-CH_2R_{60}$ wherein R_{60} represents a C_2-C_6 alkenyl group or a C_2-C_6 alkynyl group; or R_6 and R_7 are combined together to form a saturated 5- to 7-membered cyclic amino group which may contain other hetero atom(s) in the ring thereof;

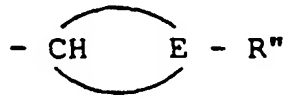
R_{40} represents a C_1-C_8 alkyl group, a substituted C_1-C_8 alkyl group or an aromatic group;

n represents 0, 1 or 2; and,

R_{20} represents a C_2-C_6 alkenyl group or a C_2-C_6 alkynyl group;

in which:

the substituent (s) of the substituted C_1-C_8 alkyl group means a halogen atom, hydroxy, a C_1-C_6 alkoxy group, cyano, carboxyl, a C_2-C_6 alkoxycarbonyl group, a C_2-C_8 alkanoyl group, an arylalkanoyl group having carbon atoms up to 10, an aroyl group having carbon atoms up to 11, an aromatic group, and $-CONR_4R_5$ in which each of R_4 and R_5 independently represents a hydrogen atom or a C_1-C_8 alkyl group or R_4 and R_5 are combined together to form a saturated 5- to 7-membered cyclic amino group which may contain other hetero atom(s) in the ring; $-NR_6R_7$; or a group shown by:



in which:

E represents a nitrogen atom or a CH group and

R" represents a hydrogen atom, a C_1-C_8 alkyl group or a substituted C_1-C_8 alkyl group substituted with hydroxy, a C_1-C_6 alkoxy group, cyano, carboxyl, a C_2-C_6 alkoxycarbonyl group, a C_2-C_8 alkanoyl group, an arylalkanoyl group having carbon atoms up to 10, an aroyl group having carbon atoms up to 11, an aromatic group, a group shown by $-NR_6R_7$, or a group shown by - $CONR_4R_5$, in which each of R_4 and R_5 independently represents a hydrogen atom or a C_1-C_8 alkyl group or R_4 and R_5 are combined together to form a saturated 5- to 7-membered cyclic amino group which may contain other hetero atom(s) therein; and the ring of

is a 3-to 8-membered saturated aliphatic ring or saturated hetero ring containing one nitrogen atom;

all of the aromatic groups hereinabove means an aryl group having carbon atoms up to 10, a 5- or 6-membered heteroaryl group containing 1 to 4 nitrogen atom(s), a 5- or 6-membered hetero-aryl group containing 1 to 2 nitrogen atom(s) and one oxygen atom or one sulfur atom, or furyl; and,

all of the aromatic groups hereinabove may be substituted with a substituent selected from the group consisting of a C_1-C_8 alkyl group, a substituted C_1-C_8 alkyl group, a halogen atom, nitro, a C_2-C_6 alkoxycarbonyl group, carboxyl and a group selected from the group shown by formulae: $-OR_3$, $-NR_6R_7$, $-CONR_6R_7$, $-SO_2NR_6R_7$ and $-S(O)_nR_{40}$;

provided that R_1 and the guanidinocarbonyl group may be substituted at any one of the 5- and 6-membered rings of the indole nucleus;

or,

a pharmaceutically acceptable acid addition salt thereof.

The respective groups in the indoloylguanidine derivatives of the general formula (1) are described below in detail.

The alkyl group refers to a linear or branched alkyl group having 8 or less carbon atoms, for example, methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl, heptyl and octyl.

The alkenyl group includes, for example, alkenyl groups of 6 or less carbon atoms, such as vinyl, allyl, propenyl, 2-propenyl, butenyl, pentenyl and hexenyl.

The alkynyl group includes, for example, alkynyl groups of 6 or less carbon atoms, such as ethynyl, propargyl, butynyl and pentynyl.

The cycloalkyl group refers to a cycloalkyl group having 3 to 7 carbon atoms, e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Typical examples of the halogen atom include fluorine, chlorine and bromine.

The acyl group refers to a linear or branched alkanoyl group having carbon atoms up to 8, e.g., acetyl, propanoyl and 2-methylpropanoyl; an arylalkanoyl group having carbon atoms up to 10, e.g., phenylacetyl and phenylpropanoyl; and an aroyl group having 11 or less carbon atoms, e.g., benzoyl, 1-naphthoyl and 2-naphthoyl.

The alkoxycarbonyl group refers to a linear or branched alkoxycarbonyl group having carbon atoms up to 6, e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and 2-propoxycarbonyl.

The aromatic group refers to an aryl or hetero-aryl group which may have a substituent. Examples of the aryl group are those having carbon atoms up to 10, e.g., phenyl, tolyl or naphthyl, and examples of the hetero-aryl group are a 5- or 6-membered aromatic group containing 1 to 4 nitrogen atoms or a 5- or 6-membered aromatic ring containing 1 to 2 nitrogen atoms and one oxygen atom or one sulfur atom, e.g., 2-, 3- or 4-pyridyl, imidazolyl, triazolyl, tetrazolyl, 2- or 3-furyl, 2- or 3-thienyl, 1-, 3- or 4-oxazolyl, and 3-, 4-or 5-isoxazolyl.

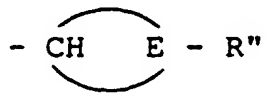
Examples of the substituent in the substituted aryl or hetero-aryl group include an alkyl group, a substituted alkyl group, a halogen atom, nitro, an alkoxycarbonyl group, carboxyl and a group shown by formula: $-OR_3$, $-NR_6R_7$, $-CONR_6R_7$, $-SO_2NR_6R_7$ or $-S(O)_nR_{40}$.

Where R_1 is a group shown by formula: $-OR_3$ wherein R_3 is an aromatic group, representative examples of the $-OR_3$ group include phenoxy and a substituted phenoxy group. Examples of the substituted phenoxy group are a phenoxy group substituted with nitro, $-NR_6R_7$ wherein R_6 and R_7 are typically a hydrogen atom or an alkyl group, or a substituted alkyl group, the substituent of which is exemplified by hydroxy or $-NR_6R_7$. Specific examples of the substituted phenoxy group are o-, m- or p-nitrophenoxy, o-, m- or p-aminophenoxy, o-, m- or p-(dimethylamino)phenoxy, o-, m- or p-(aminomethyl)phenoxy and o-, m- or p-(dimethylaminomethyl)phenoxy.

The alkoxy group refers to a linear or branched alkoxy group having carbon atoms up to 6, e.g., methoxy, ethoxy, isopropoxy and tert-butoxy.

As the saturated 5- to 7-membered cyclic amino group which is formed by combining R_6 and R_7 together and may contain other hetero atoms therein, there are, for example, a 5- to 7-membered cyclic group containing 1 to 3 nitrogen atoms and a 5- to 7-membered cyclic group containing one nitrogen atom and one oxygen atom. Specific examples of such cyclic amino group include 1-pyrrolidinyl, piperidino, 1-piperazinyl, morpholino, 4-methylmorpholino and 4-methylpiperazinyl.

Examples of the substituent in the substituted alkyl group include a cycloalkyl group, a halogen atom, hydroxy, an alkoxy group, cyano, carboxyl, an alkoxycarbonyl group, an acyl group, an aromatic group, or a group shown by formula: $-CONR_4R_5$, wherein each of R_4 and R_5 independently represents hydrogen atom or an alkyl group, or R_4 and R_5 are combined together to form a saturated 5- to 7-membered cyclic amino group which may contain other hetero atoms in the ring; $-NR_6R_7$; or a group shown by formula:



wherein:

E represents a nitrogen atom or a CH group and

R" represents a hydrogen atom, an alkyl group or a substituted alkyl group substituted with hydroxy, a C_1-C_6 alkoxy group, cyano, carboxyl, a C_2-C_6 alkoxycarbonyl group, a C_2-C_8 alkanoyl group, an arylalkanoyl group having carbon atoms up to 10, an aroyl group having carbon atoms up to 11, an aromatic group, a group shown by $-NR_6R_7$, or a group shown by $-CONR_4R_5$, in which each of R_4 and R_5 independently represents a hydrogen atom or a C_1-C_8 alkyl group or R_4 and R_5 are combined together to form a saturated 5- to 7-membered cyclic amino group which may contain other hetero atom(s) therein; and the ring of

is a 3- to 8-membered saturated aliphatic ring or saturated hetero ring containing one nitrogen atom. Particularly where R_1, R_2 and R_3 represent a substituted alkyl group, examples of the substituent include a cycloalkyl group, a halogen atom, hydroxy, an alkoxy group, carboxyl, an alkoxycarbonyl group, an acyl group, an aromatic group or a group shown by formula: $-CONR_4R_5$ or $-NR_6R_7$. Where R_6 and R_7 represent a substituted alkyl group, examples of the substituent include a cycloalkyl group, hydroxy, an alkoxy group, carboxyl, an alkoxycarbonyl group, an acyl group, an aryl group or a group shown by formula: $-CONR_4R_5$ or $-NR_4R_5$. As the alkyl moiety in the substituted alkyl group, the same examples as those for the alkyl group described above are given.

As such a substituted alkyl group, there are, for example, an alkyl group having 1 to 5 carbon atoms which is substituted with a cycloalkyl having 3 to 6 carbon atoms, a polyhaloalkyl group having 1 to 5 carbon atoms, a hydroxyalkyl group having 1 to 6 carbon atoms, an alkoxyalkyl group having 2 to 6 carbon atoms, a cyanoalkyl group having 2 to 6 carbon atoms, a carboxyalkyl group having 2 to 6 carbon atoms, an alkoxycarbonylalkyl group having 3 to 8 carbon atoms, an alkanoylalkyl group having 3 to 8 carbon atoms, an aralkyl group having carbon atoms up to 16, a phenyl- or naphthyl-C_1 to C_5 alkyl group which may be substituted, a carbamoyl-C_1 to C_3 alkyl group in which the nitrogen atom may be substituted with one or two C_1 to C_3 alkyl, an amino-C_1 to C_5 alkyl group in which the nitrogen atom may be substituted with one or two C_1 to C_3 alkyl or C_7 to C_{11} aralkyl, and a saturated 5- to 7-membered cyclic amino-C_1 to C_3 alkyl group.

Representative examples of the substituted alkyl group include:

in the case of R_1: a polyhaloalkyl group having 1 to 3 carbon atoms such as trifluoromethyl, trifluoroethyl or trichloromethyl; a hydroxyalkyl group having 1 to 6 carbon atoms such as hydroxymethyl, hydroxyethyl or 1-hydroxyethyl; and an aminoalkyl group having 1 to 5 carbon atoms such as aminomethyl, aminoethyl or 1-aminoethyl;

in the case of R_2: a hydroxyalkyl group having 1 to 6 carbon atoms such as hydroxyethyl, hydroxypropyl, hydroxybutyl, 2-hydroxypropyl or 3,4-dihydroxybutyl; an alkoxyalkyl group having 1 to 6 carbon atoms such as methoxyethyl, ethoxyethyl or methoxypropyl; a carboxyalkyl group having 2 to 6 carbon atoms such as carboxyethyl or carboxypropyl; an alkoxycarbonylalkyl group having 3 to 7 carbon atoms such as methoxycarbonylmethyl, ethoxycarbonylmethyl or methoxycarbonylethyl; a phenyl- or naphthyl-C_1 to C_5 alkyl group, wherein a phenyl or naphthyl group may be substituted with a substituent, e.g., a C_1 to c_3 alkyl group, a halogen atom, nitro, amino, hydroxy or a C_1 to C_3 alkoxy group, such as benzyl, phenylethyl, phenylpropyl, phenylbutyl or, 1- or 2-naphthylmethyl; a carbamoyl-C_1 to c_3 alkyl group in which the nitrogen atom may be substituted with one or two C_1 to C_3 alkyl groups, such as carbamoylmethyl, carbamoylethyl or dimethylcarbamoylmethyl; or, an amino-C_1 to C_5 alkyl group in which the nitrogen atom may be substituted with one or two C_1 to C_3 alkyl, such as aminoethyl, aminopropyl, dimethylaminoethyl, dimethylaminopropyl or diethylaminoethyl;

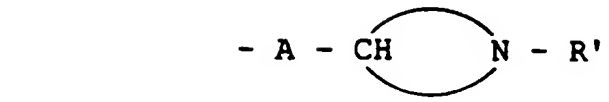
in the case of R_3 and R_{40}: a hydroxyalkyl group having 1 to 6 carbon atoms such as hydroxyethyl, hydroxypropyl, 2-hydroxypropyl, hydroxybutyl or 2,3-dihydroxybutyl; a carboxyalkyl group having 2 to 6 carbon atoms such as carboxymethyl or carboxyethyl; a phenyl-C_1 to C_5 alkyl group such as benzyl, phenylethyl or phenylpropyl; a carbamoyl-C_1 to C_3 alkyl group such as carbamoylmethyl or carbamoylethyl; an amino-C_1 to C_5 alkyl group containing one or two nitrogen atoms in which the nitrogen atom may be substituted with one or two C_1 to C_3 alkyl or C_7 to C_{11} aralkyl groups, such as aminoethyl, aminopropyl, dimethylaminoethyl, dimethylaminopropyl or benzylmethyl-aminoethyl; or a saturated 5- to 7-membered cyclic amino-C_1 to C_3 alkyl group such as 1-pyrrolidinyl-ethyl or piperidinoethyl; and,

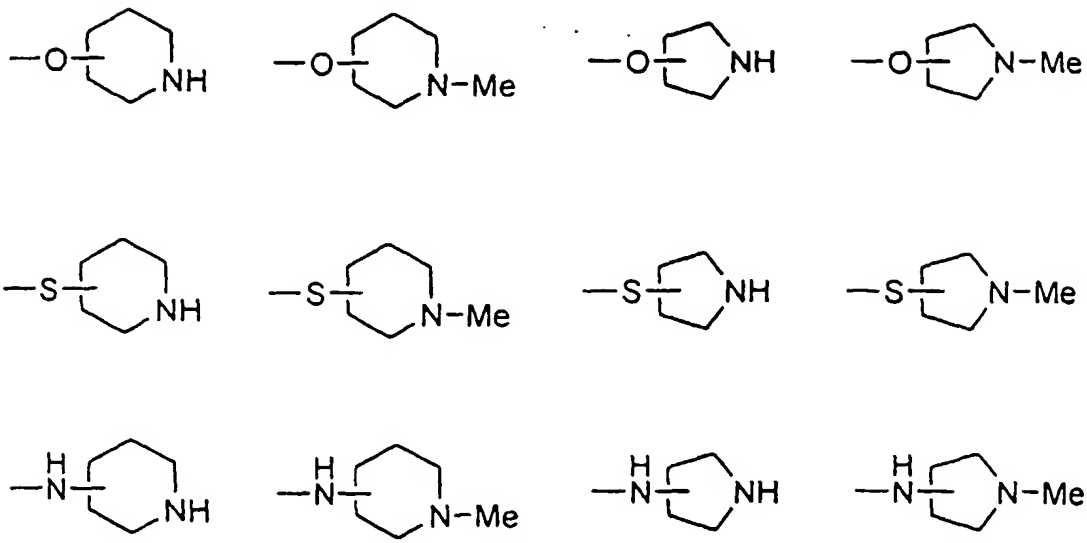
in the case of R_6 and R_7: a phenyl-C_1 to C_5 alkyl group such as phenylethyl.

Examples of the saturated 5- to 7-membered cyclic amino group which is formed by combining R_4 and R_5 together and may contain other hetero atoms in the ring thereof include the same groups as exemplified for the aforesaid cyclic amino group formed by R_6 and R_7.

Examples of the group shown by formula: $-S(O)_nR_{40}$ include an alkylsulfonyl group having carbon atoms up to 8, such as methylsulfonyl, ethylsulfonyl, propylsulfonyl or isopropylsulfonyl; and the corresponding alkylsulfinyl and alkylthio groups.

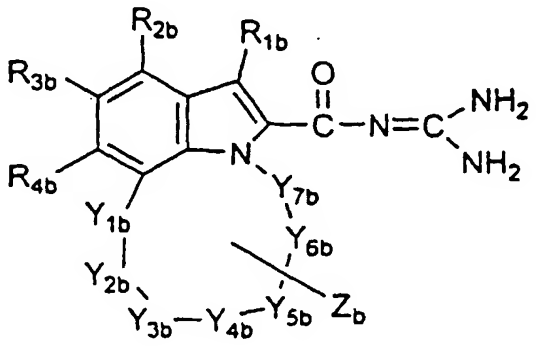
Examples of the group of include the following groups:





Among the above groups, there are preferred (piperidin-3-yl)oxy, (piperidin-4-yl)oxy, (1-methylpiperidin-3-yl)oxy, (1-methylpiperidin-4-yl)oxy, (pyrrolidin-3-yl)oxy, (1-methylpyrrolidin-3-yl)oxy, (piperidin-3-yl)thio, (piperidin-4-yl)thio, (1-methylpiperidin-3-yl)thio, (1-methylpiperidin-4-yl)thio, (pyrrolidin-3-yl)thio, (1-methylpyrrolidin-3-yl)thio, (piperidin-3-yl)amino, (piperidin-4-yl)amino, (1-methylpiperidin-3-yl)amino, (1-methylpiperidin-4-yl)amino, (pyrrolidin-3-yl)amino and (1-methylpyrrolidin-3-yl)amino.

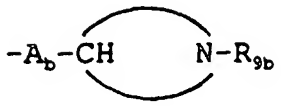
(b) The present invention relates to a pharmaceutical composition comprising a substituted guanidine derivative described in EP 787,728, which is represented by the general formula (1b):



(1b)

wherein:

R_{1b}, R_{2b}, R_{3b} and R_{4b} are independently a hydrogen atom, an unsubstituted alkyl group, a substituted alkyl group, a cycloalkyl group, a cycloalkenyl group, a saturated heterocyclic group, a halogen atom, a nitro group, a carboxyl group, an alkoxycarbonyl group, an aromatic group, an acyl group, $-OR_{5b}$, $-N(R_{6b})R_{7b}$, $-CON(R_{6b})R_{7b}$, $-SO_2N(R_{6b})R_{7b}$, $-S(O)_nR_{8b}$ wherein R_{8b} is an unsubstituted alkyl group, a substituted alkyl group or an aromatic group, and n is 0, 1 or 2, $-Q_b$-R_{ab}, or



wherein A_b is an oxygen atom or -S(O)$_n$- wherein n is as defined above or -N(R_{10b})-, R_{9b} is a hydrogen atom, an unsubstituted alkyl group, a substituted alkyl group, an acyl group or -Q_b-R_{ab}, and the ring is a 3- to 8-membered saturated heterocyclic group composed of a nitrogen atom and carbon atoms;

Y_{1b}, Y_{2b}, Y_{3b}, Y_{4b}, Y_{5b}, Y_{6b} and Y_{7b}, which may be the same or different, are independently a single bond, -CH_2-, -O-, -CO-, -C(=C(R_{11b})R_{12b})-, -S(O)$_n$- or -N(R_{10b})-, adjacent members of a group consisting of Y_{1b} through Y_{7b} being able to be taken together to represent -CH=CH-, and at least two of Y_{1b} through Y_{7b} being independently a group other than a single bond;

Z_b may be absent, or one or more Z_bs may be present and are, the same or different, independently the following substituent for a hydrogen atom bonded to any of the carbon atoms constituting the ring formed by Y_{1b} through Y_{7b}; an unsubstituted alkyl group, a substituted alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkenyl group, a substituted heterocyclic group, a halogen atom, a carboxyl group, an alkoxycarbonyl group, an aromatic group, an acyl group, -OR_{5b}, -N(R_{6b})R_{7b}, -S(O)$_n$$R_{8b}$, -C(O)N($R_{6b}$)$R_{7b}$, or -$Q_b$-$R_{ab}$, provided that when Z_b is a substituent for the hydrogen atom of -CH=CH-, Z_b is not -N(R_{6b})R_{7b} or -S(O)$_n$$R_{8b}$;

Q_b is a substituted or unsubstituted lower alkylene group;

R_{ab} is a substituted or unsubstituted vinyl group, or a substituted or unsubstituted ethynyl group;

R_{5b} is a hydrogen atom, an unsubstituted alkyl group, a substituted alkyl group, a cycloalkyl group, a cycloalkenyl group, a saturated heterocyclic group or an aromatic group;

R_{6b} and R_{7b} are independently a hydrogen atom, an unsubstituted alkyl group, a substituted alkyl group, a cycloalkyl group, a cycloalkenyl group, a saturated heterocyclic group, an aromatic group, an acyl group or -Q_b-R_{ab}, or R_{6b} and R_{7b}, when taken together with the nitrogen atom to which they are bonded, form a saturated 5- to 7-membered cyclic amino group which may contain an oxygen atom or a sulfur atom in the ring and may be substituted by one or more unsubstituted alkyl groups, substituted alkyl groups, hydroxyl groups or -OR_{5b} groups;

R_{8b} is an unsubstituted alkyl group, a substituted alkyl group or an aromatic group;

R_{10b} is a hydrogen atom, an unsubstituted alkyl group, a substituted alkyl group, a cycloalkyl group, a saturated heterocyclic group, an aromatic group, an acyl group or -Q_b-R_{ab}; and,

R_{11b} and R_{12b} are independently a hydrogen atom, an unsubstituted alkyl group, a substituted alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkenyl group, a saturated heterocyclic group, a halogen atom, a carboxyl group, an alkoxycarbonyl group, an aromatic group, an acyl group, -OR_{5b}, -N(R_{6b})R_{7b}, -C(O)N(R_{6b})R_{7b}, -S(O)$_n$$R_{8b}$ or -$Q_b$$R_{ab}$; and n is 0, 1 or 2;

or a pharmaceutically acceptable acid addition salt thereof.

The various groups in the compounds of general formula (1b) are explained below.

The alkyl group includes, for example, linear or branched alkyl groups of 8 or less carbon atoms, such as methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl, heptyl and octyl.

The cycloalkyl group may be unsubstituted or may be substituted by 1 to 4 unsubstituted alkyl groups, substituted alkyl groups, hydroxyl groups or groups of the formula -OR_{5b}, and includes, for example, 3- to 8-membered cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-methylcyclopentyl, 3-methylcyclopentyl, 2-methylcyclohexyl, 3-methylcyclohexyl, 4-methylcyclohexyl, 2-hydroxycyclopentyl, 3-hydroxycyclopentyl, 2-hydroxycyclohexyl, 3-hydroxycyclohexyl, 4-hydroxycyclohexyl, 2-(hydroxymethyl)cyclopentyl, 3-(hydroxymethyl)cyclopentyl, 2-(hydroxymethyl)cyclohexyl, 3-(hydroxymethyl)-cyclohexyl, 4-(hydroxymethyl)cyclohexyl, 2-(aminomethyl)cyclopentyl, 3-(aminomethyl)cyclopentyl, 2-(aminomethyl)cyclohexyl, 3-(aminomethyl)cyclohexyl, 4-(aminomethyl)cyclohexyl, 2-(methoxymethyl)cyclopentyl, 3-(methoxymethyl)cyclopentyl, 2-(methoxymethyl)cyclohexyl, 3-(methoxymethyl)cyclohexyl, 4-(methoxymethyl)-cyclohexyl, etc.

The cycloalkenyl group may be unsubstituted or may be substituted by 1 to 4 unsubstituted alkyl groups, substituted alkyl groups, hydroxyl groups or groups of the formula, -OR_{5b}, and includes, for example, 3- to 8-membered cycloalkenyl groups having a double bond, such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, etc.

The saturated heterocyclic group may be unsubstituted or may be substituted by 1 to 4 unsubstituted alkyl

groups, substituted alkyl groups, hydroxyl groups or group of the formula -OR_{5b}, and includes, for example, 3- to 8-membered saturated heterocyclic groups having an oxygen atom or a sulfur atom, such as 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydro-2H-pyranyl, 4-tetrahydro-4H-pyranyl, etc.

The halogen atom includes, for example, fluorine, chlorine and bromine atoms.

The alkoxycarbonyl group includes, for example, linear or branched alkoxycarbonyl group of 6 or less carbon atoms, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and 2-propoxycarbonyl.

The aromatic group includes substituted or unsubstituted aryl groups and substituted or unsubstituted heteroaryl groups. As the aryl groups, there may be exemplified aryl groups of 10 or less carbon atoms, such as phenyl, naphthyl, etc. As the heteroaryl groups, there may be exemplified 5- or 6-membered heteroaryl groups containing 1 to 4 nitrogen atoms, such as 2-, 3- or 4-pyridyl, imidazolyl, triazolyl, tetrazolyl, etc.; and 5- or 6-membered heteroaryl groups containing 0 to 2 nitrogen atoms and one oxygen atom or one sulfur atom, such as 2- or 3-furyl, 2- or 3-thienyl, 1-, 3- or 4-oxazolyl, 3-, 4- or 5-isoxazolyl, etc.

The substituent of each of the substituted aryl group and the substituted heteroaryl group includes unsubstituted alkyl groups, substituted alkyl groups, halogen atoms, nitro group, carboxyl groups, alkoxycarbonyl groups, and groups represented by the formula - OR_{5b}, -$N(R_{6b})R_{7b}$, -$CON(R_{6b})R_{7b}$, -$SO_2N(R_{6b})R_{7b}$ or -$S(O)_nR_{8b}$.

When R_{1b}, R_{2b}, R_{3b} and R_{4b} are independently a group represented by the formula -OR_{5b} wherein R_{5b} is an aromatic group, typical examples of the -OR_{5b} group are unsubstituted phenoxy groups and substituted phenoxy groups. Examples of the substituted phenoxy groups are those having as the substituent, for example, a nitro group, a -$N(R_{6b})R_{7b}$ group wherein R_{6b} and R_{7b} are independently, for instance, a hydrogen atom or an unsubstituted alkyl group, or a substituted alkyl group having as the substituent, for example, a hydroxyl group or a -$N(R_{6b})R_{7b}$ group. More specific examples of the substituted phenoxy group are o-, m- or p-nitrophenoxy, o-, m- or p-aminophenoxy, o-, m- or p-(dimethylamino)-phenoxy, o-, m- or p-(aminomethyl)phenoxy, and o-, m- or p-(dimethylaminomethyl)phenoxy.

The alkoxy group includes, for example, linear or branched alkoxy groups of 6 or less carbon atoms, such as methoxy, ethoxy, isopropoxy and tert-butoxy.

As the cyclic amino group which R_{6b} and R_{7b} form when taken together with the nitrogen atom to which they are bonded, i.e., the saturated 5- to 7-membered cyclic amino group which may contain another hetero atom in the ring, there may be exemplified 5- to 7-membered cyclic groups containing 1 to 3 nitrogen atoms and 5- to 7-membered cyclic groups containing one nitrogen atom and one oxygen atom. More specific examples of the saturated 5- to 7-membered cyclic amino group are 1-pyrrolidinyl, 1-piperidino, 1-piperazinyl, morpholino and 1-(4-methyl)piperazinyl.

The substituent on the substituted alkyl group include halogen atoms, hydroxy group, alkoxy groups, cycloalkyl groups, cyano group, carboxyl group, alkoxycarbonyl groups, acyl groups, aromatic groups, and groups shown by the formula -$CONR_{pb}R_{qb}$ (wherein R_{pb} and R_{qb} are independently a hydrogen atom or an unsubstituted alkyl group, or R_{pb} and R_{qb} being able to be taken together to represent a saturated 5- to 7-membered cyclic amino group which may contain another hetero atom in the ring), -$NR_{6b}R_{7b}$ or a group shown by formula:

wherein R" is a hydrogen atom, an unsubstituted alkyl group or a substituted alkyl group, and the ring is a 3-to 8-membered saturated heterocyclic group containing one nitrogen atom. Particularly when R_{1b}, R_{2b}, R_{3b}, R_{4b}, R_{5b}, R_{8b}, R_{11b}, R_{12b}, or Z_b is a substituted alkyl group, the substituent includes, for example, cycloalkyl groups, halogen atoms, hydroxyl group, alkoxy groups, carboxyl group, alkoxycarbonyl groups, acyl groups, aromatic groups and groups shown by formula -$CONR_{pb}R_{qb}$ or -$NR_{6b}R_{7b}$. When R_{6b}, R_{7b}, R_{9b} or R_{10b} is a substituted alkyl group, the substituent includes, for example, cycloalkyl groups, hydroxyl group, alkoxy groups, carboxyl group, alkoxycarbonyl groups, acyl groups, aryl groups and groups shown by the formula -$CONR_{pb}R_{qb}$ or -$NR_{pb}R_{qb}$. As the alkyl portion of the substituted alkyl group, there may be exemplified the same groups as those exemplified above as the alkyl group.

As such substituted alkyl groups, there may be exemplified substituted alkyl groups of 1 to 5 carbon atoms having as the substituent a cycloalkyl group of 3 to 6 carbon atoms, polyhaloalkyl groups of 1 to 5 carbon atoms, hydroxyalkyl groups of 1 to 6 carbon atoms, alkoxyalkyl groups of 2 to 6 carbon atoms, cyanoalkyl groups of 2 to 6 carbon atoms, carboxyalkyl groups of 2 to 6 carbon atoms, alkoxycarbonylalkyl groups of 3 to 8 carbon atoms, alkanoylalkyl groups of 3 to 8 carbon atoms, aroylalkyl groups of 16 or less carbon atoms, substituted or unsubstituted phenyl- or naphthyl-C_1-C_5 alkyl groups, carbamoyl-C_1-C_3 alkyl groups which may have one or two C_1-C_3 alkyl

groups as a substituent(s) on the nitrogen atom, amino-C_1-C_5 alkyl groups which may have one or two C_1-C_3 alkyl or C_7-C_{11} aralkyl groups as a substituent(s) on the nitrogen atom, and saturated 5- to 7-membered cyclic amino-C_1-C_3 alkyl groups.

Typical examples of the substituted alkyl group are polyhaloalkyl groups of 1 to 3 carbon atoms, such as trifluoromethyl, trifluoroethyl or trichloromethyl; hydroxyalkyl groups of 1 to 6 carbon atoms, such as hydroxymethyl, hydroxyethyl or 1-hydroxyethyl; aminoalkyl groups of 1 to 5 carbon atoms, such as aminomethyl, aminoethyl or 1-aminoethyl; alkoxyalkyl groups of 1 to 6 carbon atoms, such as methoxyethyl, ethoxyethyl or methoxypropyl; carboxyalkyl groups of 2 to 6 carbon atoms, such as carboxyethyl or carboxypropyl; alkoxycarbonylalkyl groups of 3 to 7 carbon atoms, such as methoxycarbonylmethyl, ethoxycarbonylmethyl or methoxycarbonylethyl; phenyl- or naphthyl-C_1-C_5 alkyl groups (which may have in the phenyl or naphthyl portion a substituent such as a C_1-C_3 alkyl group, halogen atom, nitro group, amino group, hydroxyl group, C_1-C_3 alkoxy group or the like) such as benzyl, phenylethyl, phenylpropyl, phenylbutyl or, 1- or 2-naphthylmethyl; carbamoyl-C_1-C_3 alkyl groups which may have one or two C_1-C_3 alkyl groups as a substituent(s) on the nitrogen atom, for example, carbamoylmethyl, carbamoylethyl or dimethylcarbamoyl-methyl; amino-C_1-C_5 alkyl groups which may have one or two C_1-C_3 alkyl groups or C_7-C_{11} aralkyl groups as a substituent(s) on the nitrogen atom, for example, aminoethyl, aminopropyl, dimethylaminoethyl, dimethylaminopropyl, diethylaminoethyl or N-methyl-N-benzylaminoethyl; and saturated 5- to 7-membered cyclic amino-C_1-C_3 alkyl groups such as 1-pyrrolidinyl-ethyl or piperidinoethyl. In the case of R_{6b} and R_{7b}, typical examples of the substituted alkyl group are phenyl-C_1-C_5 alkyl groups such as phenylethyl.

As the substituent on the lower alkylene group for Q_b and the substituent on the vinyl or ethynyl group for R_{ab}, there may be exemplified unsubstituted alkyl groups, substituted alkyl groups, cycloalkyl groups, cycloalkenyl groups, saturated heterocyclic groups, carboxyl group, alkoxycarbonyl groups, aromatic groups, and groups represented by the formula $-CON(R_{6b})R_{7b}$.

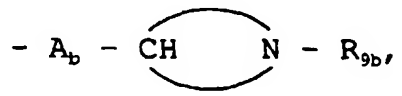
The lower alkylene group includes, for example, alkylene groups of 6 or less carbon atoms, such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, etc.

The acyl group includes, for example, formyl group; alkanoyl groups of 2 to 6 carbon atoms, such as acetyl, propanoyl, etc.; cycloalkanecarbonyl groups of 3 to 6 carbon atoms, such as cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, etc.; cycloalkenecarbonyl groups of 3 to 6 carbon atoms, such as cyclopentenecarbonyl, cyclohexenecarbonyl, etc.; aroyl groups of 6 to 10 carbon atoms, such as benzoyl, toluoyl, naphthoyl, etc.; saturated heterocyclic ring-carbonyl groups having a 5- or 6-membered saturated heterocyclic group containing one or two hetero atoms selected from the group consisting of nitrogen atom, oxygen atom and sulfur atom, for example, 2-piperidinecarbonyl, 3-morpholinecarbonyl, etc.; and heteroaryl acyl groups having a 5- or 6-membered heteroaryl ring containing one or two hetero atoms selected from the group consisting of nitrogen atom, oxygen atom and sulfur atom, for example, furoyl, thenoyl, nicotinoyl, isonicotinoyl, etc.

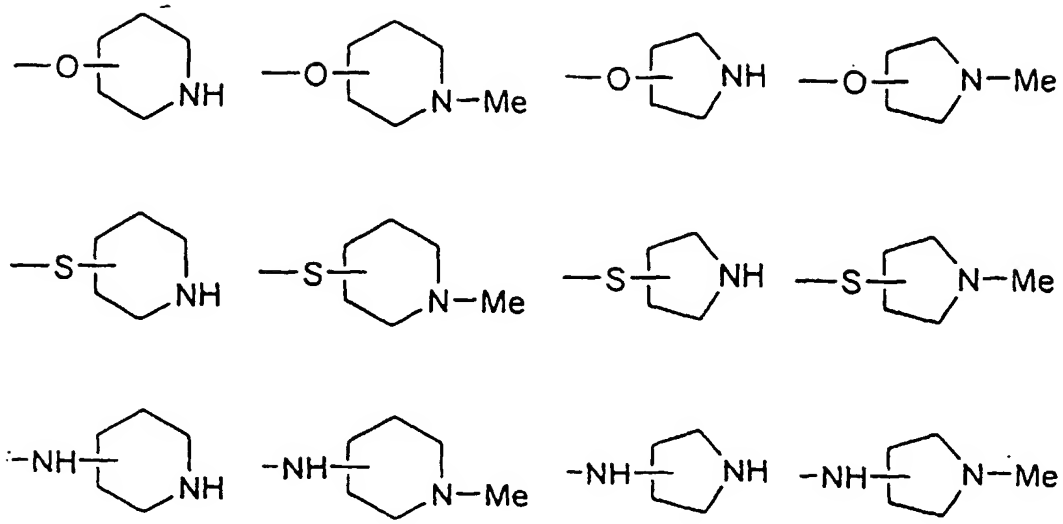
As the cyclic amino group which R_{pb} and R_{bq} form when taken together, i.e., the saturated 5- to 7-membered cyclic amino group which may contain another hetero atom in the ring, there may be exemplified the same groups as those exemplified above as the cyclic amino group formed by R_{6b} and R_{7b}.

The group represented by the formula $-S(O)_nR_{8b}$ includes, for example, alkylsulfonyl groups of 8 or less carbon atoms, such as methylsulfonyl, ethylsulfonyl, propylsulfonyl or isopropylsulfonyl; and the corresponding alkylsulfinyl groups and alkylthio groups.

As the group represented by the formula:



there may be exemplified groups represented by the following formulas:



Preferred examples of the aforesaid group are (piperidin-3-yl)oxy, (piperidin-4-yl)oxy, (1-methylpiperidin-3-yl)oxy, (1-methylpiperidin-4-yl)oxy, (pyrrolidin-3-yl)oxy, (1-methylpyrrolidin-3-yl)oxy, (piperidin-3-yl)thio, (piperidin-4-yl)thio, (1-methylpiperidin-3-yl)thio, (1-methylpiperidin-4-yl)thio, (pyrrolidin-3-yl)thio, (1-methylpyrrolidin-3-yl)thio, (piperidin-3-yl)amino, (piperidin-4-yl)amino, (1-methylpiperidin-3-yl)amino, (1-methylpiperidin-4-yl)amino, (pyrrolidin-3-yl)amino and (1-methylpyrrolidin-3-yl)amino.

The alkenyl group includes, for example, alkenyl groups of 6 or less carbon atoms, such as vinyl, allyl, propenyl, 2-propenyl, butenyl, pentenyl and hexenyl.

The alkynyl group includes, for example, alkynyl groups of 6 or less carbon atoms, such as ethynyl, propargyl, butynyl and pentynyl.

As Y_{1b}, Y_{2b}, Y_{3b}, Y_{4b}, Y_{5b}, Y_{6b} and Y_{7b}, the following may be exemplified.

1. One of Y_{1b} through Y_{7b} is $-CH_2-$, -O-, -CO-, $-C(=C(R_{11b})R_{12b})-$, $-S(O)_n-$ or $-N(R_{10b})-$, another is $-CH_2-$, and the five others, which may be the same or different, are independently a single bond or $-CH_2-$. More specific examples of Y_{1b} through Y_{7b} are as follows.

1-1. Y_{1b} is $-CH_2-$, -O-, -CO-, $-C(=C(R_{11b})R_{12b})-$, $-S(O)_n-$ or $-N(R_{10b})-$, Y_{2b} is $-CH_2-$, and Y_{3b} through Y_{7b}, which may be the same or different, are independently a single bond or $-CH_2-$.

1-2. Y_{7b} is -O-, -CO-, $-C(=C(R_{11b})R_{12b})-$, Y_{6b} is $-CH_2-$, and Y_{1b} through Y_{5b}, which may be the same or different, are independently a single bond or $-CH_2-$.

1-3. Y_{1b} and Y_{7b} are $-CH_2-$, one of Y_{2b}, Y_{3b}, Y_{4b}, Y_{5b} and Y_{6b} is $-CH_2-$, -O-, $-C(=C(R_{11b})R_{12b})-$, $-S(O)_n-$ or $-N(R_{10b})-$, and the four others, which may be the same or different, are independently a single bond or $-CH_2-$.

1-4. Y_{1b} is $-CH_2-$, -O-, -CO-, $-C(=C(R_{11b})R_{12b})-$, $-S(O)_n-$ or $-N(R_{10b})-$, Y_{2b} through Y_{4b} are independently $-CH_2-$, and Y_{5b} and Y_{6b} are independently a single bond.

2. Any adjacent two members of a group consisting of Y_{1b} through Y_{7b} are taken together to represent -CH=CH-, the four others, which may be the same or different, are independently a single bond or $-CH_2-$, and Y_{7b} is a single bond, -O-, -CO-, $-C(=C(R_{11b})R_{12b})-$or $-CH_2-$.

More specific examples of Y_{1b} through Y_{7b} are as follows.

2-1. $-Y_{1b}-Y_{2b}-$ is -CH=CH-.

2-2. Y_{1b} is $-CH_2-$, and $-Y_{2b}-Y_{3b}-$ is -CH=CH-.

2-3. Y_{1b} and Y_{2b} are independently $-CH_2-$, and $-Y_{3b}-Y_{4b}-$ is -CH=CH-.

2-4. Y_{1b}, Y_{2b} and Y_{3b} are $-CH_2-$, and $-Y_{4b}-Y_{5b}-$ is -CH=CH-.

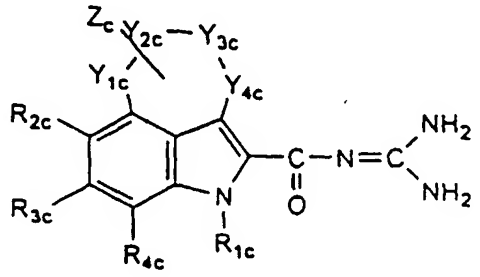
3. Y_{1b} is -O- or $-N(R_{10b})-$, one of Y_{2b} through Y_{7b} is -CO-, and the five others, which may be the same or different, are independently a single bond or $-CH_2-$.

More specific examples of Y_{1b} through Y_{7b} are as follows.

3-1. Y_{2b} is -CO-.
3-2. Y_{2b} is $-CH_2-$, and Y_{3b} is -CO-.
3-3. Y_{2b} and Y_{3b} are $-CH_2-$, and Y_{4b} is -CO-.
3-4. Y_{2b}, Y_{3b} and Y_{4b} are $-CH_2-$, and Y_{5b} is -CO-.
3-5. Y_{2b}, Y_{3b}, Y_{4b} and Y_{5b} are $-CH_2-$, and Y_{6b} is - CO-.

Preferred examples of Y_{1b} through Y_{7b} are such that two of five, in particular, two to four, of Y_{1b} through Y_{7b} are independently a single bond and the others independently a group other than a single bond. More preferably, two or three of Y_{1b} through Y_{7b} are independently a single bond, and the others are groups other than a single bond.

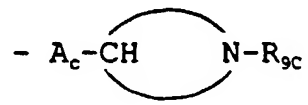
(c) The present invention relates to a pharmaceutical composition comprising a substituted guanidine derivative described in Japanese Patent KOKAI (Laid-Open) No. 9-291076, which is represented by the general formula (1c):



(1c)

wherein

R_{1c} is a hydrogen atom, an unsubstituted alkyl group, a substituted alkyl group, a cycloalkyl group, a cycloalkenyl group, a saturated heterocyclic group, an aromatic group, $-OR_{5c}$, an acyl group or $-Q_c-R_{ac}$;
R_{2c}, R_{3c} and R_{4c} are independently a hydrogen atom, an unsubstituted alkyl group, a substituted alkyl group, a cycloalkyl group, a cycloalkenyl group, a saturated heterocyclic group, a halogen atom, a nitro group, a carboxyl group, an alkoxycarbonyl group, an aromatic group, $-OR_{5c}$, $-N(R_{6c})R_{7c}$, $-CON(R_{6c})R_{7c}$, $-SO_2N(R_{6c})R_{7c}$, $-S(O)_nR_{8c}$, an acyl group, $-Q_c-R_{ac}$, or



wherein the ring is a 3- to 8-membered saturated heterocyclic group composed of a nitrogen atom and carbon atoms;
Y_{1c}, Y_{2c}, Y_{3c} and Y_{4c} are as follows:

(1) one of Y_{1c}, Y_{2c}, Y_{3c} and Y_{4c} is a methylene group, a carbonyl group, an oxygen atom, $-S(O)_n-$, $-N(R_{10c})-$ or $-C(=C(R_{11c})(R_{12c}))-$, two others are independently a methylene group, and the remaining one is a single bond or a methylene group, or,
(2) any adjacent two members of a group consisting of Y_{1c}, Y_{2c}, Y_{3c}, and Y_{4c} are taken together to represent a vinylene group (-CH=CH-) or $-CON(R_{10c})-$, another is a methylene group, a carbonyl group, an oxygen atom, $-S(O)_n-$, $-N(R_{10c})-$ or $-C(=C(R_{11c})(R_{12c}))-$, and the remaining one is a single bond or a methylene group, provided that the oxygen atom, nitrogen atom and sulfur atom are not directly bonded to the vinylene group;

Z_c is a substituent which may be substituted for at least one hydrogen atom (for example, one or two hydrogen atoms) bonded to any of the carbon atoms constituting the ring formed by Y_{1c}, Y_{2c}, Y_{3c}, and Y_{4c}, namely, Z_c may be absent, or one or more Zs may be present and are independently a substituent selected from the group consisting of unsubstituted alkyl groups, substituted alkyl groups, alkenyl

groups, alkynyl groups, cycloalkyl groups, cycloalkenyl groups, saturated heterocyclic groups, halogen atoms, carboxyl groups, alkoxycarbonyl groups, aromatic groups, $-OR_{5c}$, $-N(R_{6c})R_{7c}$, $-CON(R_{6c})R_{7c}$, $-S(O)_nR_{8c}$, acyl groups and $-Q_c-R_{ac}-$;

A_c is an oxygen atom, $-S(O)_n-$ or $-N(R_{10c})-$;

Q_c is a substituted or unsubstituted lower alkylene group;

R_{ac} is a substituted or unsubstituted vinyl group, or a substituted or unsubstituted ethynyl group;

R_{5c} is a hydrogen atom, an unsubstituted alkyl group, a substituted alkyl group, a cycloalkyl group, a cycloalkenyl group, a saturated heterocyclic group or an aromatic group;

R_{6c} and R_{7c} are independently a hydrogen atom, an unsubstituted alkyl group, a substituted alkyl group, a cycloalkyl group, a cycloalkenyl group, a saturated heterocyclic group, an aromatic group, an acyl group or $-Q_c-R_{ac}$, or R_{6c} and R_{7c}, when taken together with the nitrogen atom to which they are bonded, form a saturated 5- to 7-membered cyclic amino group which may contain an oxygen atom or a sulfur atom in the ring and may be substituted by one or more (for example, two) unsubstituted alkyl groups, substituted alkyl groups, hydroxyl groups or $-OR_{5c}$ groups;

R_{8c} is an unsubstituted alkyl group, a substituted alkyl group or an aromatic group;

R_{9c} is a hydrogen atom, an unsubstituted alkyl group, a substituted alkyl group, an acyl group or $-Q_c-R_{ac}$,

R_{10c} is a hydrogen atom, an unsubstituted alkyl group, a substituted alkyl group, a cycloalkyl group, a saturated heterocyclic group, an aromatic group, an acyl group or $-Q_c-R_{ac}$; and,

R_{11c} and R_{12c} are independently a hydrogen atom, an unsubstituted alkyl group, a substituted alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkenyl group, a saturated heterocyclic group, a halogen atom, a carboxyl group, an alkoxycarbonyl group, an aromatic group, $-OR_{5c}$, $-N(R_{6c})R_{7c}$, $-CON(R_{6c})R_{7c}$, $-S(O)_nR_{8c}$, an acyl group or $-Q_c-R_{ac}-$; and,

n is 0, 1 or 2; or a pharmaceutically acceptable acid addition salt thereof.

The various groups in the compounds of general formula (1c) are explained below.

The alkyl group includes, for example, linear or branched alkyl groups of 8 or less carbon atoms, such as methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl, heptyl and octyl.

The cycloalkyl group may be unsubstituted or may be substituted by 1 to 4 unsubstituted alkyl groups, substituted alkyl groups, hydroxyl groups or groups of the formula $-OR_{5c}$, and includes, for example, 3- to 8-membered cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-methylcyclopentyl, 3-methylcyclopentyl, 2-methylcyclohexyl, 3-methylcyclohexyl, 4-methylcyclohexyl, 2-hydroxycyclopentyl, 3-hydroxycyclopentyl, 2-hydroxycyclohexyl, 3-hydroxycyclohexyl, 4-hydroxycyclohexyl, 2-(hydroxymethyl)cyclopentyl, 3-(hydroxymethyl)cyclopentyl, 2-(hydroxymethyl)cyclohexyl, 3-(hydroxymethyl)-cyclohexyl, 4-(hydroxymethyl)cyclohexyl, 2-(aminomethyl)cyclopentyl, 3-(aminomethyl)cyclopentyl, 2-(aminomethyl)cyclohexyl, 3-(aminomethyl)cyclohexyl, 4-(aminomethyl)cyclohexyl, 2-(methoxymethyl)cyclopentyl, 3-(methoxymethyl)cyclopentyl, 2-(methoxymethyl)cyclohexyl, 3-(methoxymethyl)cyclohexyl, 4-(methoxymethyl)-cyclohexyl, etc.

The cycloalkenyl group may be unsubstituted or may be substituted by 1 to 4 unsubstituted alkyl groups, substituted alkyl groups, hydroxyl groups or groups of the formula, $-OR_{5c}$, and includes, for example, 3- to 8-membered cycloalkenyl groups having a double bond, such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, etc.

The saturated heterocyclic group may be unsubstituted or may be substituted by 1 to 4 unsubstituted alkyl groups, substituted alkyl groups, hydroxyl groups or group of the formula $-OR_{5c}$, and includes, for example, 3- to 8-membered saturated heterocyclic groups having an oxygen atom or a sulfur atom, such as 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydro-2H-pyranyl, 4-tetrahydro-4H-pyranyl, etc.

The halogen atom includes, for example, fluorine, chlorine and bromine atoms.

The alkoxycarbonyl group includes, for example, linear or branched alkoxycarbonyl group of 6 or less carbon atoms, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and 2-propoxycarbonyl.

The aromatic group includes substituted or unsubstituted aryl groups and substituted or unsubstituted heteroaryl groups. As the aryl groups, there may be exemplified aryl groups of 10 or less carbon atoms, such as phenyl, naphthyl, etc. As the heteroaryl groups, there may be exemplified 5- or 6-membered heteroaryl groups containing 1 to 4 nitrogen atoms, such as 2-, 3- or 4-pyridyl, pyrrolyl, imidazolyl, triazolyl, tetrazolyl, etc.; and 5- or 6-membered heteroaryl groups containing 0 to 2 nitrogen atoms and one oxygen atom or one sulfur atom, such as 2- or 3-furyl, 2- or 3-thienyl, 1-, 3- or 4-oxazolyl, 3-, 4- or 5-isoxazolyl, etc. The substituent of each of the substituted

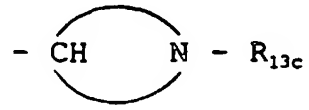
aryl group and the substituted heteroaryl group includes unsubstituted alkyl groups, substituted alkyl groups, halogen atoms, nitro group, carboxyl groups, alkoxycarbonyl groups, and groups represented by the formula $-OR_{5c}$, $-N(R_{6c})R_{7c}$, $-CONR_{6c}R_{7c}$, $-SO_2NR_{6c}R_{7c}$ or $-S(O)_nR_{8c}$.

When R_{1c}, R_{2c}, R_{3c} and R_{4c} are independently a group represented by the formula $-OR_{5c}$ wherein R_{5c} is an aromatic group, typical examples of the $-OR_{5c}$ group are unsubstituted phenoxy groups and substituted phenoxy groups. Examples of the unsubstituted phenoxy groups are those having as the substituent, for example, a nitro group, a $-NR_{6c}R_{7c}$ group (wherein R_{6c} and R_{7c} are independently, for instance, a hydrogen atom or an unsubstituted alkyl group), or a substituted alkyl group having as the substituent, for example, a hydroxyl group or a $-NR_{6c}R_{7c}$ group. More specific examples of the substituted phenoxy groups are o-, m- or p-nitrophenoxy, o-, m- or p-aminophenoxy, o-, m- or p-(dimethylamino)phenoxy, o-, m- or p-(aminomethyl)phenoxy, and o-, m- or p-(dimethylaminomethyl)phenoxy.

The alkoxy group includes, for example, linear or branched alkoxy groups of 6 or less carbon atoms, such as methoxy, ethoxy, isopropoxy, tert-butoxy, etc.

As the cyclic amino group which R_{6c} and R_{7c} form when taken together with the nitrogen atom to which they are bonded, i.e., the saturated 5- to 7-membered cyclic amino group which may contain another hetero atom in the ring, there may be exemplified 5- to 7-membered cyclic groups containing 1 to 3 nitrogen atoms and 5- to 7-membered cyclic groups containing one nitrogen atom and one oxygen atom. More specific examples of the saturated 5- to 7-membered cyclic amino group are 1-pyrrolidinyl, 1-piperidino, 1-piperazinyl, 4-morpholino and 1-(4-methyl)piperazinyl.

The substituent on the substituted alkyl group include halogen atoms, hydroxy group, alkoxy groups, cycloalkyl groups, cyano group, carboxyl group, alkoxycarbonyl groups, aromatic groups, acyl groups and groups shown by the formula $-CONR_{pc}R_{qc}$, wherein R_{pc} and R_{qc} are independently a hydrogen atom or an unsubstituted alkyl group, or R_{pc} and R_{qc} being able to be taken together to represent a saturated 5- to 7-membered cyclic amino group which may contain another hetero atom in the ring, $-NR_{6c}R_{7c}$ or a group shown by formula:



wherein R_{13c} is a hydrogen atom, an unsubstituted alkyl group or a substituted alkyl group, and the ring is a 3-to 8-membered saturated heterocyclic group containing one nitrogen atom. Particularly when any of R_{1c}, R_{2c}, R_{3c}, R_{4c}, R_{5c}, R_{8c}, R_{9c}, R_{12c} and Z_c is a substituted alkyl group, the substituent includes, for example, cycloalkyl groups, halogen atoms, hydroxyl group, alkoxy groups, carboxyl group, alkoxycarbonyl groups, acyl groups, aromatic groups and groups shown by the formula $-CONR_{pc}R_{qc}$ or $-NR_{6c}R_{7c}$. When any of R_{6c}, R_{7c}, R_{10c}, R_{11c} and R_{13c} is a substituted alkyl group, the substituent includes, for example, cycloalkyl groups, hydroxyl group, alkoxy groups, carboxyl group, alkoxycarbonyl groups, acyl groups, aryl groups, and groups shown by the formula $-CONR_{pc}R_{qc}$ or $-NR_{pc}R_{qc}$. As the alkyl portion of the substituted alkyl group, there may be exemplified the same groups as those exemplified above as the alkyl group.

As such substituted alkyl groups, there may be exemplified substituted alkyl groups of 1 to 5 carbon atoms having as the substituent a cycloalkyl group of 3 to 6 carbon atoms, polyhaloalkyl groups of 1 to 5 carbon atoms, hydroxyalkyl groups of 1 to 6 carbon atoms, alkoxyalkyl groups of 2 to 6 carbon atoms, cyanoalkyl groups of 2 to 6 carbon atoms, carboxyalkyl groups of 2 to 6 carbon atoms, alkoxycarbonylalkyl groups of 3 to 8 carbon atoms, alkanoylalkyl groups of 3 to 8 carbon atoms, aroylalkyl groups of 16 or less carbon atoms, substituted or unsubstituted phenyl- or naphthyl-C_1-C_5 alkyl groups, carbamoyl-C_1-C_3 alkyl groups which may have one or two C_1-C_3 alkyl groups as a substituent(s) on the nitrogen atom, amino-C_1-C_5 alkyl groups which may have one or two C_1-C_3 alkyl or C_7-C_{11} aralkyl groups as a substituent(s) on the nitrogen atom, and saturated 5- to 7-membered cyclic amino-C_1-C_3 alkyl groups.

Typical examples of the substituted alkyl group are polyhaloalkyl groups of 1 to 3 carbon atoms, such as trifluoromethyl, trifluoroethyl or trichloromethyl; hydroxyalkyl groups of 1 to 6 carbon atoms, such as hydroxymethyl, hydroxyethyl or 1-hydroxyethyl; aminoalkyl groups of 1 to 5 carbon atoms, such as aminomethyl, aminoethyl or 1-aminoethyl; alkoxyalkyl groups of 1 to 6 carbon atoms, such as methoxyethyl, ethoxyethyl or methoxypropyl; carboxyalkyl groups of 2 to 6 carbon atoms, such as carboxyethyl or carboxypropyl; alkoxycarbonylalkyl groups of 3 to 7 carbon atoms, such as methoxycarbonylmethyl, ethoxycarbonylmethyl or methoxycarbonylethyl; phenyl- or naphthyl-C_1-C_5 alkyl groups (which may have in the phenyl or naphthyl portion a substituent such as a C_1-C_3 alkyl group, halogen atom, nitro group, amino group, hydroxyl group, C_1-C_3 alkoxy group or the like) such as benzyl, phenylethyl, phenylpropyl, phenylbutyl or, 1- or 2-naphthylmethyl; carbamoyl-C_1-C_3 alkyl groups which may have one or two C_1-C_3 alkyl groups as a substituent(s) on the nitrogen atom, for example, carbamoylmethyl, carbamoylethyl or dimethylcarbamoylmethyl; amino-C_1-C_5 alkyl groups which may have one or two C_1-C_3 alkyl groups or C_7-C_{11} aralkyl groups as a substituent(s) on the nitrogen atom, for example, aminoethyl, aminopropyl, dimethylaminoethyl,

dimethylaminopropyl, diethylaminoethyl or N-methyl-N-benzylaminoethyl; and saturated 5-to 7-membered cyclic amino-C_1-C_3 alkyl groups such as 1-pyrrolidinylethyl or piperidinoethyl. In the case of R_{6c} and R_{7c}, typical examples of the substituted alkyl group are phenyl-C_1-C_5 alkyl groups such as phenylethyl.

As the substituent on the lower alkylene group for Q_c and the substituent on the vinyl or ethynyl group for R_{ac}, there may be exemplified unsubstituted alkyl groups, substituted alkyl groups, cycloalkyl groups, cycloalkenyl groups, saturated heterocyclic groups, carboxyl group, alkoxycarbonyl groups, aromatic groups, and groups represented by the formula $-CON(R_{6c})R_{7c}$.

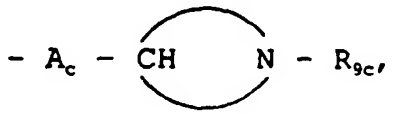
The lower alkylene group includes, for example, alkylene groups of 6 or less carbon atoms, such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, etc.

The acyl group includes, for example, formyl group; alkanoyl groups of 2 to 6 carbon atoms, such as acetyl, propanoyl, etc.; cycloalkanecarbonyl groups of 3 to 6 carbon atoms, such as cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, etc.; cycloalkenecarbonyl groups of 3 to 6 carbon atoms, such as cyclopentenecarbonyl, cyclohexenecarbonyl, etc.; aroyl groups of 6 to 10 carbon atoms, such as benzoyl, toluoyl, naphthoyl, etc.; saturated heterocyclic ring-carbonyl groups having a 5- or 6-membered saturated heterocyclic group containing one or two hetero atoms selected from the group consisting of nitrogen atom, oxygen atom and sulfur atom, for example, 2-piperidinecarbonyl, 3-morpholinecarbonyl, etc.; and heteroaromatic acyl groups having a 5- or 6-membered heteroaromatic ring containing one or two hetero atoms selected from the group consisting of nitrogen atom, oxygen atom and sulfur atom, for example, furoyl, thenoyl, nicotinoyl, isonicotinoyl, etc.

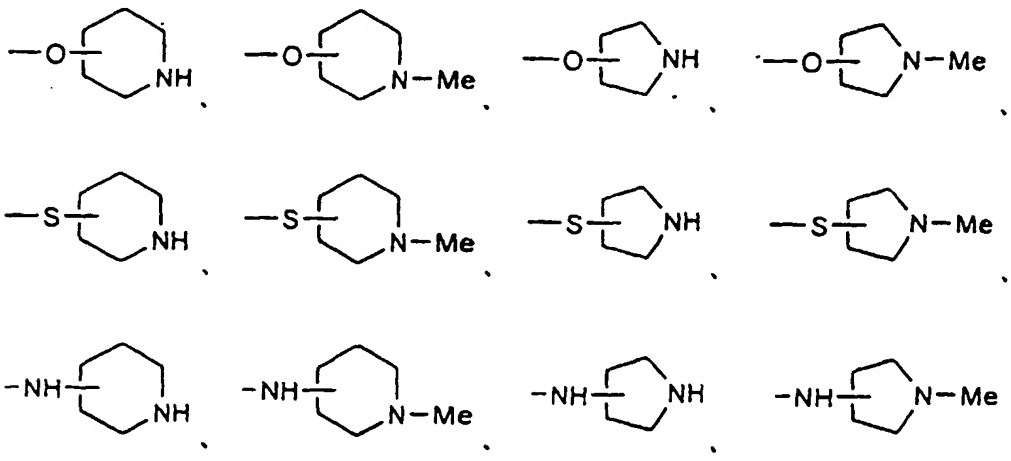
As the cyclic amino group which R_{pc} and R_{qc} form when taken together, i.e., the saturated 5- to 7-membered cyclic amino group which may contain another hetero atom in the ring, there may be exemplified the same groups as those exemplified above as the cyclic amino group formed by R_{6c} and R_{7c}.

The group represented by the formula $-S(O)_nR_{8c}$ includes, for example, alkylsulfonyl groups of 8 or less carbon atoms, such as methylsulfonyl, ethylsulfonyl, propylsulfonyl or isopropylsulfonyl; and alkylsulfinyl groups and alkylthio groups, which correspond to the alkylsulfonyl groups.

As the group represented by the formula:



there may be exemplified groups represented by the following formulas:

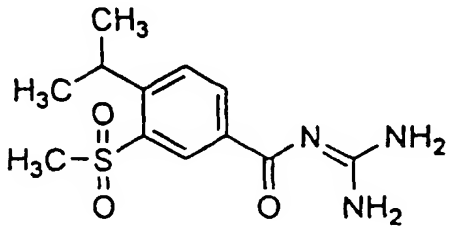


Preferred examples of the aforesaid group are (piperidin-3-yl)oxy, (piperidin-4-yl)oxy, (1-methylpiperidin-3-yl)oxy, (1-methylpiperidin-4-yl)oxy, (pyrrolidin-3-yl)oxy, (1-methylpyrrolidin-3-yl)oxy, (piperidin-3-yl)thio, (piperidin-4-yl)thio, (1-methylpiperidin-3-yl)thio, (1-methylpiperidin-4-yl)thio, (pyrrolidin-3-yl)thio, (1-methylpyrrolidin-2-yl)thio, (piperidin-3-yl)amino, (piperidin-4-yl)amino, (1-methylpiperidin-3-yl)amino, (1-methylpiperidin-4-yl)amino, (pyrrolidin-3-yl)amino and (1-methylpyrrolidin-3-yl)amino.

The alkenyl group includes, for example, alkenyl groups of 6 or less carbon atoms, such as vinyl, allyl, propenyl, 2-propenyl, butenyl, pentenyl and hexenyl.

The alkynyl group includes, for example, alkynyl groups of 6 or less carbon atoms, such as ethynyl, propargyl, butynyl and pentynyl.

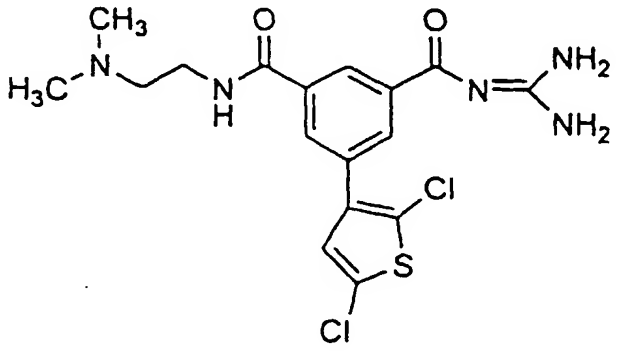
(d) The present invention relates to pharmaceutical compositions comprising Compound (d) represented by formula (1d):



(1d)

or pharmaceutically acceptable acid addition salts thereof, in particular, the methanesulfonate (Code No. HOE-642, cariporide, namely, 4-isopropyl-3-methylsulfonylbenzoylguanidine methanesulfonate).

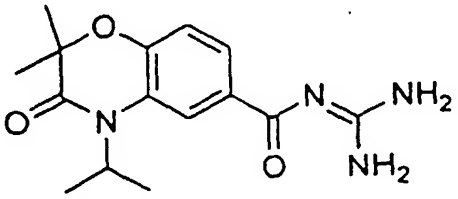
(e) The present invention relates to pharmaceutical compositions comprising Compound (e) represented by formula (1e):



(1e)

or pharmaceutically acceptable acid addition salts thereof, in particular, the dihydrochloride (Code No. FR183998).

(f) The present invention relates to pharmaceutical compositions comprising Compound (f) represented by formula (1f):

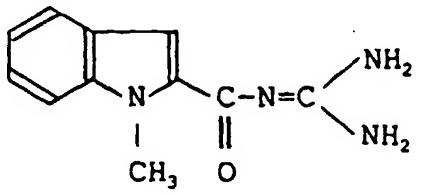


(1f)

or pharmaceutically acceptable acid addition salts thereof, in particular, the methanesulfonate (Code No. KBR-9032).

Of the compounds described above, particularly preferred are Compounds (g) and (h) shown below.

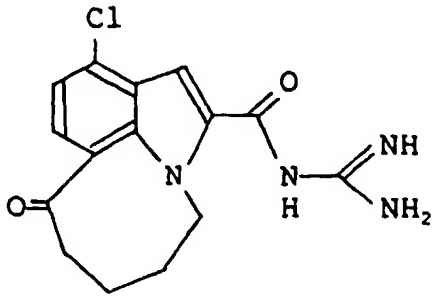
(g) 1-Methyl-2-indoloylguanidine represented by the formula (1g) described in Japanese Patent KOKAI (Laid-Open) No. 8-208602:



(1g)

or salts thereof, more preferably the methanesulfonate thereof.

(h) N-(Aminoiminomethyl)-5,6,7,8-tetrahydro11-chloro-8-oxo-4H-azocino[3,2,1-hi]indole-2-carboxamide of the formula (1h) described in EP 787,728:



(1h)

or salt thereof, more preferably, the methanesulfonate thereof.

[0015] Throughout the present specification, the compounds represented by the general formulas (1), (1b) and (1c) and the compounds of the formulas (1d), (1e), (1f), (1g) and (1h) are described using the formulas (1), (1b), (1c), (1d), (1e), (1f), (1g) and (1h) but tautomers of these compounds are also present since the guanidine portions are tautomeric. More specifically, the tautomer of acylguanidine group: $-C(O)N=C(NH_2)_2$ in which the guanidine portion takes diaminomethyleneamino as well as that of $-C(O)NH-C(=NH)NH_2$ in which the guanidine portion takes aminoiminomethylamino are present in the respective compounds. These tautomeric compounds are different only in their chemical formation state but have the same pharmacological effects. Therefore, the compounds which may be used in the pharmaceutical compositions of the present invention include these tautomeric isomers.

[0016] The compounds of the general formulas (1), (1b) and (1c) also include those having optically asymmetric centers. Thus, these compounds may be obtained in the racemic form, or can be obtained in the optically active form in the case that optically active starting materials are employed. If necessary and desired, the racemic compounds thus obtained may resolved chemically or physically into enantiomers by known methods. Preferably, the racemic compounds are subjected to a reaction using an optically active resolving agent to convert into the diastereomers. The diastereomers in different configurations may be resolved in a conventional manner, for example, by fractional crystallization.

[0017] The compounds represented by the general formulas (1), (1b) and (1c) and the compounds represented by the formulas (1d), (1e), (1f), (1g) and (1h) may be converted into acid addition salts with pharmaceutically acceptable inorganic acids or organic acids, if necessary and desired. Examples of such acid addition salts are salts with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid; salts with organic acids such as formic acid, acetic acid, fumaric acid, maleic acid, oxalic acid, citric acid, malic acid, tartaric acid, aspartic acid or glutamic acid; salts with sulfonic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, hydroxybenzenesulfonic acid, dihydroxybenzenesulfonic acid, etc.

[0018] The compounds represented by the general formulas (1), (1b) and (1c) and the compounds represented by the formulas (1d), (1e), (1f), (1g) and (1h), and acid addition salts thereof may take the form of the anhydrides, hydrates and solvates thereof.

[0019] As the Na^+/H^+ exchanger inhibitors which can be used in the pharmaceutical compositions of the present invention, compounds described in a publication, such as the one described in the following publications may also be used to achieve the objects of the present invention, which publications are, for example:

[0020] Japanese Patent KOKAI (Laid-Open) Nos. 7-10839, 8-208602, 9-268172, 9-291076, 9-227496, 9-221465, 9-169719, 9-169718, 9-169721, 9-169723, 9-124584, 9-52823, 9-31045, 8-319226, 8-311012, 8-259515, 8-225514, 8-99950, 8-92215, 8-12643, 8-27093, 7-304729, 7-291927, 7-224022, 7-109251, 7-76566, 7-89938, 6-345715, 6-345643, 6-256291, 6-234730, 6-256290, 6-239828, 6-228082, 6-116230, 5-339228, 8-291131, 8-41028, 7-206823, 7-82234, 7-145149, 9-124583, 9-52876, 8-311011, 8-245560, 8-269001, 8-283232, 8-73427, 8-59598, 8-59602, 8-188568, 8-27113, 7-267926, 8-225513, 9-77753, 9-59245, 9-67332, 9-67340 and 8-277269; PCT KOKAI (Laid-Open) Nos. 6-509798, 9-505035, 9-504535, 8-511243 and 9-500895; European Patent (EP) Nos. 794172, 794171, 790245, 765868 and 787728; German Patent (DE) Nos. 19548708 and 19601303, WO Nos. 9711055, 9640728, 9604241, 9725310 and 9727183.

[0021] The compounds having the Na^+/H^+ exchange system inhibition activity and salts thereof, which are used in the present invention, may be prepared by the methods described in the patent publications supra, etc.

[0022] The pharmaceutical composition of the present invention, useful for the treatment of ischemic brain damage, comprises as the active ingredient the compound having the Na^+/H^+ exchange system inhibition activity or salt thereof. These compounds having the Na^+/H^+ exchange system inhibition activity or salt thereof may freely take optional forms in the pharmaceutical composition without any restriction. This compound or salt thereof may be formulated into a pharmaceutical preparation suitable for oral or parenteral administration. The compound or salt thereof described above may also be employed in the pharmaceutical preparation after the compound or salt is dissolved in distilled water or a buffer solution. In the case that the active compound is used in the form of injection, a solution, suspension or emulsion of the compounds is prepared, using conventional substances for this purpose, for example, a solubilizer, an emulsifier or other additives. Solvents available for the purpose of the present invention are, for example, water, physiological saline, an alcohol such as ethanol or propanol, or a sugar solution such as a glucose solution or a mannitol solution, and a mixture of the various solvents described above. The pharmaceutical composition of the present invention may further contain, if necessary and desired, other pharmaceutical additives, such as a surfactant, an emulsifier and a stabilizer. The pharmaceutical composition of the present invention contains the active compound in a concentration of, for example, approximately 0.1 to 10 wt%. The composition in a non-parenteral preparation may be prepared, for example, by mixing the active compound with appropriate carriers conventionally acceptable for this purpose, for example, an excipient, a stabilizer, a diluent, a binder, etc. and then treating the resulting mixture in a conventional manner into an appropriate dosage mode, such as tablets, coated tablets, capsules, granules, powders, syrup or suspensions. The excipient that may be used in the pharmaceutical composition of the present invention are, for example, gum arabic, magnesia, magnesium carbonate, calcium phosphate, lactose, glucose or starch, especially corn starch.

[0023] The dosage and frequency of administration may vary and may be determined preferably depending upon the age, body weight, condition and administration route. In general, the composition of the present invention is administered in a daily dose of 0.1 to 2000 mg, preferably 1 to 200 mg, per day for adult in a single dose or by multiple dose.

[0024] The present invention is described below more specifically with reference to Examples but is not deemed to be limited thereto.

[0025] Compound 1 used in Examples 1 and 4 is 1-methyl-2-indoloylguanidine methanesulfonate, which is described in Example 240 of Japanese Patent KOKAI (Laid-Open) No. 8-208602, namely, the methanesulfonate of the compound represented by the formula (1g); Compound 2 used in Examples 2 and 5 is 1,4-dimethyl-2-indoloylguanidine methanesulfonate, which is described in Example 241 of Japanese Patent KOKAI (Laid-Open) No. 8-208602, and Compound 3 used in Examples 3 and 6 is N-(aminoiminomethyl)-5,6,7,8-tetrahydro-11-chloro-8-oxo-4H-azocino[3,2,1-hi]indole-2-carboxamide methanesulfonate monohydrate, which is described in Example 22 of Japanese Patent KOKAI (Laid-Open) No. 10-237073, namely, the methanesulfonate of the compound represented by the formula (1h).

Example 1

Effect of $Na^{\pm}/H^{\pm}$ exchanger inhibitor on the infarcted area induced in transient ischemic rats

[0026] Male rats were anesthetized with halothane mixed with nitrous oxide. The cervical region was dissected to ligate the left external carotid artery and the left common carotid artery. Occlusion was induced for 2 hours in the control section at the origin of the middle cerebral artery by inserting a nylon thread through the left internal carotid artery to reach the left middle deutocerebral artery. Reperfusion through the middle cerebral artery was established by withdrawing the nylon thread. The test compound was intravenously given to the animals in a volume of 1 ml/kg at 30 minutes after the occlusion. As the test compound, a solution of Compound 1 (1 mg/ml) in 8% polyethylene glycol #400 was used. For control, the vehicle (8% polyethylene glycol #400) containing no active compound was used. The animals were decapitated 22 hours after reperfusion and the brain was removed. Coronal sections of 2 mm thick were prepared

in the ipsilateral hemisphere from 3 mm anterior to 5 mm posterior of the bregma. The sections were stained with 2,3,5-triphenyltetrazolium chloride for photographing. The photographs were scanned with a scanner (GT-8000, Epson) for computer-based image analysis (software used, Ep Scan Mac 1. 40). The rate of the infarcted area of each section in the left hemisphere was analyzed by a computer (software used, NIH image 1.59). The pharmacological effect was evaluated by mean percentage of the infarcted areas in the five sections obtained in one rat.

[0027] By the left middle cerebral artery occlusion for 2 hours, mean infarcted area of 47.9 ± 3.6% in each section (mean ± standard error in 9 cases) was observed 22 hours after reperfusion in the control group. In the group treated with Compound 1, mean infarcted area observed in each section was only 35.4 ± 3.1% (mean ± standard error in 8 cases, p<5%, Student's t-test). The data reveals that the infarcted area was significantly reduced in the Compound 1-treated group, as compared to the control group. The infarcted area of each section in the left hemisphere is expressed by mean ± standard error, which is shown in Fig. 1.

Example 2

Effect of $Na^{\pm}/H^{\pm}$ exchanger inhibitor on the infarcted area induced in transient ischemic rats

[0028] Compound 2 was elucidated for the effect on the infarcted area in a manner similar to that of Example 1. The test compound was intraperitoneally given 30 minutes before the occlusion to the animals in a volume of 1 ml/kg. As the test compound, a solution of Compound 2 (1 mg/ml) in 8% polyethylene glycol #400 was used. For control, the vehicle (8% polyethylene glycol #400) containing no active compound was used.

[0029] In the control group, the mean percentage of the infarcted area in each section was 49.5 ± 4.1% (mean ± standard error in 6 cases). In the drug-treated group, the infarcted area observed in each section was only 26.6 ± 3.1% (mean ± standard error in 5 cases). The data reveals that the infarcted area was significantly reduced in the drug-treated group with p<1% (by Student's t-test), as compared to the control group. The infarcted area of each section in the left hemisphere is expressed by mean percentage with standard error, which is shown in Fig. 2.

Example 3

Effect of $Na^{\pm}/H^{\pm}$ exchanger inhibitor on the infarcted area induced in transient ischemic rats

[0030] Compound 3 was elucidated for the effect on the infarcted area in a manner similar to that of Example 1. The test compound was intraperitoneally given immediately after the occlusion to the animals in a volume of 1 ml/kg. As the test compound, a solution of Compound 3 (1 mg/ml) in 8% polyethylene glycol #400 was used. For control, the vehicle (8% polyethylene glycol #400) containing no active compound was used.

[0031] In the control group, the mean percentage of the infarcted area in each section was 55.4 ± 2.1% (mean ± standard error in 14 cases). In the drug-treated group, the infarcted area observed in each section was only 45.2 ± 2.2% (mean ± standard error in 13 cases). The data reveals that the infarcted area was significantly reduced in the drug-treated group with p<5% (by Student's t-test), as compared to the control group. The infarcted area of each section in the left hemisphere is expressed by mean percentage with standard error, which is shown in Fig. 3.

Example 4

Effect of $Na^{\pm}/H^{\pm}$ exchanger inhibitor on brain edema induced in rats with transient ischemia

[0032] Male rats were anesthetized with halothane mixed with nitrous oxide. The cervical region was dissected to ligate the left external carotid artery and the left common carotid artery. Occlusion was induced for 2 hours in the control section at the origin of the middle cerebral artery by inserting a nylon thread through the left internal carotid artery to reach the left middle deutocerebral artery. Reperfusion through the middle cerebral artery was established by withdrawing the nylon thread. The test compound was intravenously given to the animals an hour after the occlusion in a volume of 1 ml/kg. As the test compound, a solution of Compound 1 (0.3 mg/ml or 1 mg/ml) in 8% polyethylene glycol #400 was used. For control, the vehicle alone (8% polyethylene glycol #400) containing no active compound was used. The animals were decapitated 4 hours after reperfusion and the brain was removed. Coronal sections of 4 mm thick were prepared in the ipsilateral hemisphere from 1 mm anterior to 3 mm posterior of the bregma. After the wet weight (W) of each section was weighed, the section was dried in an oven at 110°C for 24 hours and then its dry weight (D) was weighed. The brain water content (WC) was calculated according to the following equation.

$$WC = (W - D) / W \times 100$$

In the normal control group, the brain water content was 79.9 ± 0.1% (mean ± standard error in 15 cases); however, by reperfusion following the occlusion, the brain water content in the control group increased to 83.3 ± 0.3% (mean + standard error in 15 cases). The drug-treated groups showed the brain water content of 82.6 ± 0.3% and 82.2 ± 0.3% in 0.3 mg/kg and 1 mg/kg, respectively (mean ± standard error both in 16 cases). The results indicate that the drug-treated groups significantly prevented the increase in water content with $p<1\%$, when compared to the control group (by Williams' multiple comparison). The results of mean brain water content with standard error obtained in the respective groups are shown in Fig. 4.

Example 5

Effect of $Na^{\pm}/H^{\pm}$ exchanger inhibitor on brain edema induced in rats with transient ischemia

[0033] Compound 2 was elucidated for the effect on brain edema in a manner similar to that of Example 4. The test compound was intravenously given immediately after the reperfusion to the animals in a volume of 1 ml/kg. As the test compound, a solution of Compound 2 (1 mg/ml) in 8% polyethylene glycol #400 was used. For control, the vehicle (8% polyethylene glycol #400) containing no active compound was used.

[0034] In the normal control group, the brain water content was found to be 78.7 ± 0.1% (mean ± standard error in 8 cases). By reperfusion following the ischemia, the brain water content in the control group increased to 81.9 ± 0.4% (mean ± standard error in 11 cases). In the drug-treated group, the brain water content was found to be 82.0 ± 0.4% (mean ± standard error in 11 cases); no significant effect of preventing the increase in brain water content was noted. The results of mean brain water content with standard error in each section are shown in Fig. 5.

Example 6

Effect of $Na^{\pm}/H^{\pm}$ exchanger inhibitor an brain edema induced in rats with transient ischemia

[0035] Compound 3 was elucidated for the effect on brain edema in a manner similar to that of Example 4. The test compound was intravenously given immediately after the reperfusion to the animals in a volume of 1 ml/kg. As the test compound, a solution of Compound 3 (0.3 mg/ml or 1 mg/ml) in 8% polyethylene glycol #400 was used. For control, the vehicle alone (8% polyethylene glycol #400) containing no active compound was used.

[0036] In the normal control group, the brain water content was found to be 79.2 ± 0.2% (mean ± standard error in 7 cases). By reperfusion following the ischemia, the brain water content in the control group increased to 82.8 ± 0.3% (mean ± standard error in 10 cases). In the drug-treated groups, the brain water content was found to be 82.4 ± 0.3% and 81.7 ± 0.4%, respectively, in 0.3 mg/kg and 1 mg/kg (mean ± standard error in 9 cases and 11 cases, respectively). The data reveal the tendency that the drug-treated groups prevented the increase in brain water content, as compared to the control group. The results of mean brain water content with standard error in each section are shown in Fig. 6.

[0037] It is established by these experiments in the Examples above that the Na^+/H^+ exchanger inhibitors exhibit good effects on ischemia-induced brain edema and cerebral infarction and therefore, effective for the treatment of ischemic brain damage.

[0038] The present invention thus provides the pharmaceutical compositions comprising the Na^+/H^+ exchanger inhibitors which are effective for the treatment of ischemic brain damage.

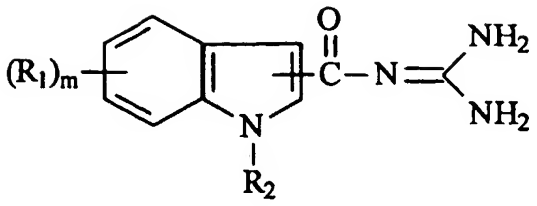
Claims

1. Use of a compound which has Na^+/H^+ exchange system inhibition activity, or a pharmaceutically acceptable salt thereof, in the manufacture of a pharmaceutical composition for the treatment of ischemic brain damage.

2. Use according to claim 1 wherein the compound is a substituted guanidine derivative, or a pharmaceutical acceptable acid addition salt thereof, which has Na^+/H^+ exchange system inhibition activity.

3. Use according to claim 1 or 2 wherein the compound is selected from the following compounds (a), (b), (c), (d), (e) and (f):

   Compound (a) is an indoloyl guanidine derivative of formula (1):

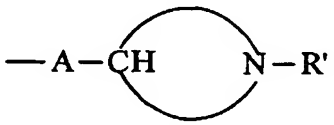


(1)

in which:

m is 1, 2, 3, 4 or 5;

each R_1, which may be the same or different, is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, a halogen, nitro, C_2-C_8 alkanoyl, arylalkanoyl having up to 10 carbon atoms, aroyl having up to 11 carbon atoms, carboxyl, C_2-C_6 alkoxycarbonyl, an aromatic group, a group of formula: $-OR_3$, $-NR_6R_7$, $-SO_2NR_6R_7$ or $-S(O)_nR_{40}$, or a group of formula:



wherein A is oxygen or a group of formula: $-S(O)_n-$ or $-N(R_{50})-$ wherein R_{50} is hydrogen or C_1-C_8 alkyl, R' is hydrogen, C_1-C_8 alkyl or substituted C_1-C_8 alkyl; and the ring is a saturated C_1-C_8 alkyl; and the ring is a saturated 3 to 8-membered hereto ring containing one nitrogen atom;

R_2 is hydrogen, C_1-C_8 alkyl, substituted C_1-C_8 alkyl, C_3-C_7 cycloalkyl, hydroxy, C_1-C_6 alkoxy, an aromatic group or a group of formula: $-CH_2R_{20}$;

R_3 is hydrogen, C_1-C_8 alkyl, substituted C_1-C_8 alkyl, C_3-C_7 cycloalkyl, an aromatic group or a group of formula: $-CR_2R_{30}$, in which R_{30} is C_2-C_6 alkenyl or C_2-C_6 alkynyl;

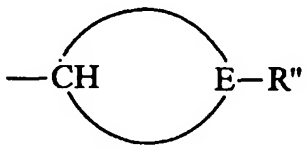
each of R_6 and R_7, which are the same or different, is independently hydrogen, C_1-C_8 alkyl, substituted C_1-C_8 alkyl, C_3-C_7 cycloalkyl, C_2-C_8 alkanoyl, arylalkanoyl having up to 10 carbon atoms, aroyl having up to 11 carbon atoms, an aromatic group or a group of formula $-CH_2R_{60}$ wherein R_{60} is C_2-C_6 alkenyl or C_2-C_6 alkynyl; or R_6 and R_7 form, together with the N atom to which they are attached, a saturated 5- to 7-membered cyclic amino group which may contain other hetero atom(s) in the ring thereof;

R_{40} is C_1-C_8 alkyl, substituted C_1-C_8 alkyl or an aromatic group;

n is 0, 1 or 2; and

R_{20} is C_2-C_6 alkenyl or C_2-C_6 alkynyl; and wherein:

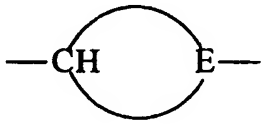
a substituted C_1-C_8 alkyl group as defined above is C_1-C_8 alkyl substituted by halogen, hydroxy, C_1-C_6 alkoxy, cyano, carboxyl, C_2-C_6 alkoxycarbonyl, C_2-C_8 alkanoyl, arylalkanoyl having up to 10 carbon atoms, aroyl having up to 11 carbon atoms, an aromatic group or $-CONR_4R_5$ in which each of R_4 and R_5, which are the same or different, is independently hydrogen or C_1-C_8 alkyl, or R_4 and R_5 form, together with the N atom to which they are attached, a saturated 5- to 7-membered cyclic amino group which may contain other hetero atom(s) in the ring; $-NR_6R_7$; or a group of formula:



in which:

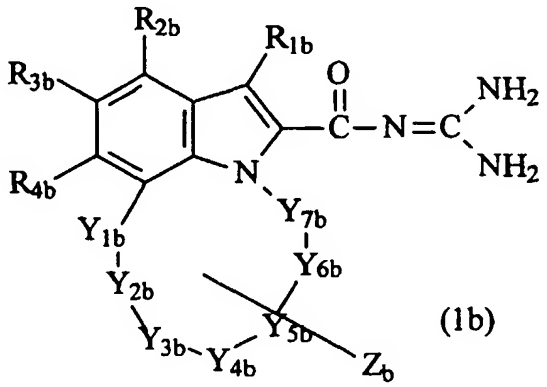
E is nitrogen or CH, and,

R" is hydrogen, C_1-C_8 alkyl or C_1-C_8 alkyl substituted by hydroxy, C_1-C_6 alkoxy, cyano, carboxyl, C_2-C_6 alkoxycarbonyl, C_2-C_8 alkanoyl, arylalkanoyl having up to 10 carbon atoms, aroyl having up to 11 carbon atoms, an aromatic group, a group of formula $-NR_6R_7$, or a group of formula $CONR_4R_5$ in which each of R_4 and R_5, which are the same or different, is independently hydrogen or C_1-C_8 alkyl, or R_4 and R_5 form together with the N atom to which they are attached a saturated 5- to 7-membered cyclic amino group which may contain other hetero atom(s) therein; and the ring of formula



is a 3- to 8-membered saturated aliphatic ring or saturated hereto ring containing one nitrogen atom;
an aromatic group as defined above is an aryl group having up to 10 carbon atoms, a 5- or 6-membered heteroaryl group containing 1 to 4 nitrogen atom(s), a 5- or 6-membered hetero-aryl group containing 1 to 2 nitrogen atom(s) and one oxygen atom or one sulfur atom, or furyl, the said aromatic said group being unsubstituted or substituted by C_1-C_8 alkyl, substituted C_1-C_8 alkyl as defined above, halogen, nitro, C_2-C_6 alkoxycarbonyl, carboxyl or a group of formula: - OR_3, $-NR_6R_7$, $-CONR_6R_7$, $-SO_2NR_6R_7$ or $-S(O)_nR_{40}$ wherein R_3, R_6, R_7, n and R_{40} are as defined above;
and wherein each R_1 and the guanidinocarbonyl moiety may occupy any position on the 5- or 6-membered ring of the indole nucleus;
or a pharmaceutically acceptable acid addition salt thereof;

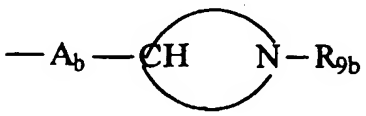
Compound (b)is a substituted guanidine derivative of formula (1b):



(1b)

in which:

each of R_{1b}, R_{2b}, R_{3b} and R_{4b}, which are the same or different, is hydrogen, alkyl, cycloalkyl, cycloalkenyl, a heterocyclic or aromatic group, each said group being unsubstituted or substituted, or is halogen, nitro, carboxyl, alkoxycarbonyl, acyl, $-OR_{5b}$, $-N(R_{6b})R_{7b}$, $-CON(R_{6b})R_{7b}$, $-SO_2N(R_{6b})R_{7b}$ or $-S(O)_nR_{8b}$ wherein R_{8b} is alkyl or an aromatic group as defined above and n is 0, 1 or 2, $-Q_b$-R_{ab}, or



wherein A_b is an oxygen atom or $-S(O)_n$- wherein n is as defined above or $-N(R_{10b})$-, R_{9b} is hydrogen,

unsubstituted or substituted alkyl, acyl or -Q_b-R_{ab}-, and the ring is a 3- to 8-membered saturated heterocyclic group composed of a nitrogen atom and carbon atoms;

each of Y_{1b}, Y_{2b}, Y_{3b}, Y_{4b}, Y_{5b}, Y_{6b} and Y_{7b}, which are the same or different is independently a single bond, -CH_2-, -O-, -CO-, -C(=C(R_{11b})R_{12b})-, -S(O)$_n$- or -N(R_{10b})-, or adjacent members of Y_{1b} to Y_{7b} represent together -CH=CH-, and at least two of Y_{1b} to Y_{7b} being independently a group other than a single bond;

Z_b may be absent or one or more Z_bs, which may be the same or different, may be bonded to one or more of the carbon atoms constituting the ring formed by Y_{1b} to Y_{7b}, the or each Z_b being unsubstituted or substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted heterocyclic, a halogen, carboxyl, alkoxycarbonyl, an aromatic group, acyl, -OR_{5b}, -N(R_{6b})R_{7b}, -S(O)$_n$$R_{8b}$, -C(O)N($R_{6b}$)$R_{7b}$, or -$Q_b$-$R_{ab}$, provided that when Z_b replaces a hydrogen atom in -CH=CH- Z_b is not -N(R_{6b})R_{7b} or -S(O)$_n$$R_{8b}$;

Q_b is substituted or unsubstituted lower alkylene;

R_{ab} is vinyl or ethynyl, both of which are substituted or unsubstituted;

R_{5b} is hydrogen, unsubstituted alkyl, substituted alkyl, cycloalkyl, cycloalkenyl, a saturated heterocyclic group or an aromatic group;

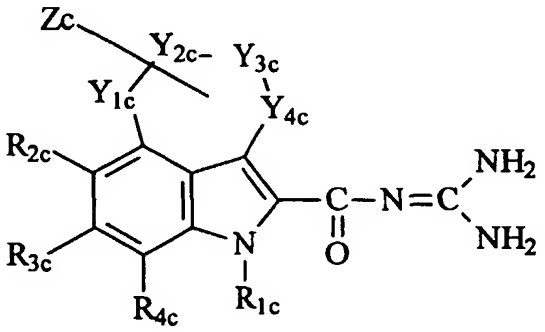
R_{6b} and R_{7b}, which are the same or different, are each hydrogen, unsubstituted alkyl, substituted alkyl, cycloalkyl, cycloalkenyl, saturated heterocyclic, an aromatic group, acyl or -$Q_b$$R_{ab}$, or R_{6b} and R_{7b}, when taken together with the nitrogen atom to which they are bonded, form a saturated 5- to 7-membered cyclic amino group which may contain an oxygen atom or a sulfur atom in the ring and may be substituted by one or more unsubstituted or substituted alkyl, hydroxyl or -OR_{5b} groups;

R_{8b} is an unsubstituted or substituted alkyl or an aromatic group;

R_{10b} is hydrogen, unsubstituted or substituted alkyl, cycloalkyl, saturated heterocyclic, an aromatic group, acyl or Q_b-R_{ab}; and;

R_{11} and R_{12b}, which are the same or different, are each hydrogen, unsubstituted or substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, saturated heterocyclic, a halogen atom, carboxyl, alkoxycarbonyl, an aromatic group, acyl, -OR_{5b}, -N(R_{6b})R_{7b},- C(O)N(R_{6b})R_{7b}, -S(O)$_n$$R_{8b}$ or -Q_b-R_{ab}; and n is 0, 1 or 2; or a pharmaceutically acceptable acid addition salt thereof;

Compound (c) is substituted guanidine derivative of formula (1c):

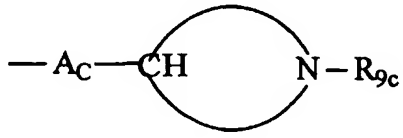


(1c)

in which:

R_{1c} is hydrogen, unsubstituted or substituted alkyl, cycloalkyl, cycloalkenyl, saturated heterocyclic, an aromatic group, -OR_{5c}, acyl or -Q_c-R_{ac};

R_{2c}, R_{3c} and R_{4c}, which are the same or different, are independently hydrogen, unsubstituted or substituted alkyl, cycloalkyl, cycloalkenyl, saturated heterocyclic, a halogen, nitro, carboxyl, alkoxycarbonyl, an aromatic group, -OR_{5c}, -N(R_{6c})R_{7c}, -CON(R_{6c})R_{7c}, - SO_2N(R_{6c})R_{7c}, -S(O)$_n$$R_{8c}$ wherein R_{8c} is unsubstituted or substituted alkyl or an aromatic group, and n is 0, 1 or 2, acyl, -Q_c-R_{ac}, or



wherein the ring is a 3- to 8- membered saturated heterocyclic group composed of a nitrogen atom and carbon atoms;

Y_{1c}, Y_{2c}, Y_{3c} and Y_{4c} are defined as follows:

(1) one of Y_{1c},Y_{2c},Y_{3c} and Y_{4c} is methylene, carbonyl, an oxygen atom, $-S(O)_n-$, $-N(R_{10c})-$ or $-C(=C(R_{11c})(R_{12c}))-$, two others are independently a methylene group, and the remaining one is a single bond or a methylene group, or

(2) any adjacent two members of Y_{1c},Y_{2c},Y_{3c} and Y_{4c} together form a vinylene group (-CH=CH-) or $-CON(R_{10c})-$, another is methylene, carbonyl, an oxygen atom, $-S(O)_n-$, $-N(R_{10c})-$ or $-C(=C(R_{11c})(R_{12c}))-$, and the remaining one is a single bond or a methylene group, provided that the oxygen atom, nitrogen atom and sulfur atom are not directly bonded to the vinylene group;

Z_c may be absent or one or more Z_cs, which may be the same or different, may be bonded to one or more of the carbon atoms constituting the ring formed by Y_{1c} to Y_{4c}, the or each Z_c being unsubstituted or substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, saturated heterocyclic, halogen, carboxyl, alkoxycarbonyl, an aromatic group, $-OR_{5c}$, $-N(R_{6c})R_{7c}$, $-CON(R_{6c})R_{7c}$, $-S(O)_nR_{8c}$, acyl, or $-Q_c-R_{ac}-$;

A_c is an oxygen atom, $-S(O)_n-$ wherein n is as defined above or $-N(R_{10c})-$;

Q_c is substituted or unsubstituted lower alkylene;

R_{ac} is vinyl or ethynyl,both of which are substituted or unsubstituted;

R_{5c} is hydrogen, unsubstituted or substituted alkyl, cycloalkyl, cycloalkenyl, saturated heterocyclic or an aromatic group;

R_{6c} and R_{7c}, which may be the same or different, are independently hydrogen, unsubstituted or substituted alkyl, cycloalkyl, cycloalkenyl, saturated heterocyclic, an aromatic group, acyl or $-Q_c-R_{ac}$, or R_{6c} and R_{7c}, when taken together with the nitrogen atom to which they are bonded, form a saturated 5- to 7-membered cyclic amino group which may contain an oxygen atom or a sulfur atom in the ring and may be substituted by one or more unsubstituted or substituted alkyl, hydroxyl or $-OR_{5c}$ groups;

R_{8c} is unsubstituted or substituted alkyl or an aromatic group;

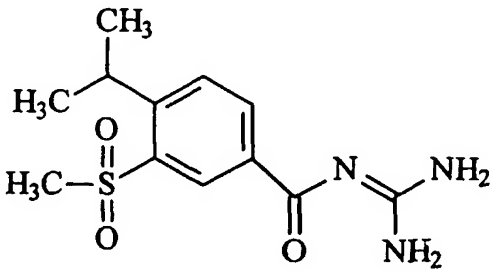
R_{9c} is hydrogen, unsubstituted or substituted alkyl, acyl or $-Q_c-R_{ac}$,

R_{10} is hydrogen, unsubstituted or substituted alkyl, cycloalkyl, saturated heterocyclic, an aromatic group, acyl or $-Q_c-R_{ac}$; and

R_{11c} and R_{12c}, which may be the same or different, are independently hydrogen, unsubstituted or substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, saturated heterocyclic, a halogen, carboxyl, alkoxycarbonyl, an aromatic group, $-OR_{5c}$, $-N(R_{6c})R_{7c}$, $-CON(R_{6c})R_{7c}$, $-S(O)_nR_{8c}$, acyl or $-Q_c-R_{ac}-$; and n is 0, 1 or 2;

or a pharmaceutically acceptable acid addition salt thereof;

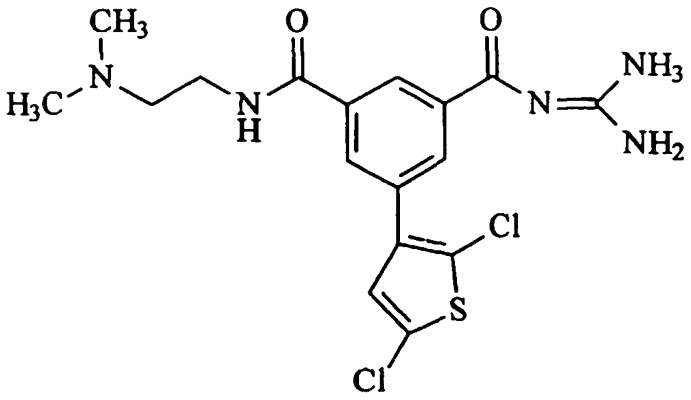
Compound (d) is a substituted guanidine derivative of formula:



(1d)

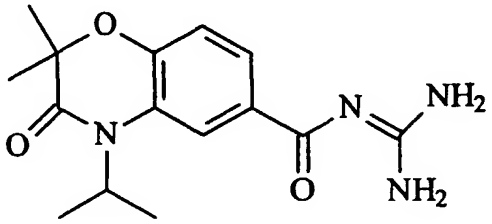
or a pharmaceutically acceptable acid addition salt thereof;

Compound (e) is a substituted guanidine derivative of formula (1e):



(1e)

or a pharmaceutically acceptable acid addition salt thereof; and,
Compound (f) is a substituted guanidine derivative of formula (1f):



(1f)

or a pharmaceutically acceptable acid addition salt thereof.

4. Use according to claim 3, wherein the compound is Compound (a).

5. Use according to claim 3, wherein the compound is Compound (b).

6. Use according to claim 3, wherein the compound is selected from 1-methyl-2-indoloylguanidine, N-(aminoiminomethyl)-5,6,7,8-tetrahydro-11-chloro-8-oxo-4H-azocino[3,2,1-hi]indole-2-carboxamide, 1-methyl-2-indoloylguanidine and N-(aminoiminomethyl)-5,6,7,8-tetrahydro-11-chloro-8-oxo-4H-azocino[3,2,1-hi]indole-2-carboxamide, and the pharmaceutically acceptable acid addition salts thereof.

7. Use according to any one of claim 1 to 6 wherein the ischemic brain damage is cerebral infarction.

8. Use according to any one of claims 1 to 6 wherein the ischemic brain damage is cerebral embolism.

9. Use according to any one of claims 1 to 6, wherein the ischemic brain damage is cerebral thrombus.

FIG.1

EFFECT OF COMPOUND 1 ON INFARCTED AREA IN TRANSIENT ISCHEMIC RATS

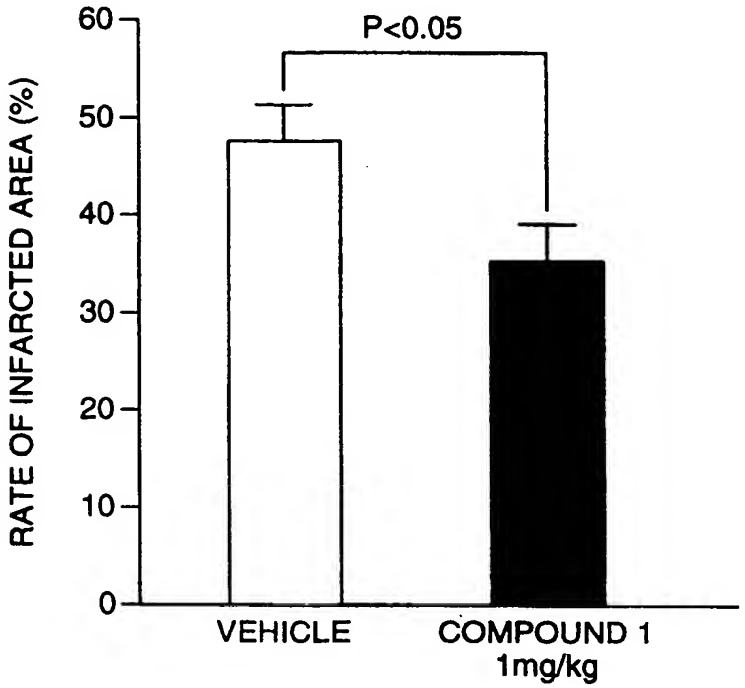


FIG.2

EFFECT OF COMPOUND 2 ON INFARCTED AREA IN TRANSIENT ISCHEMIC RATS

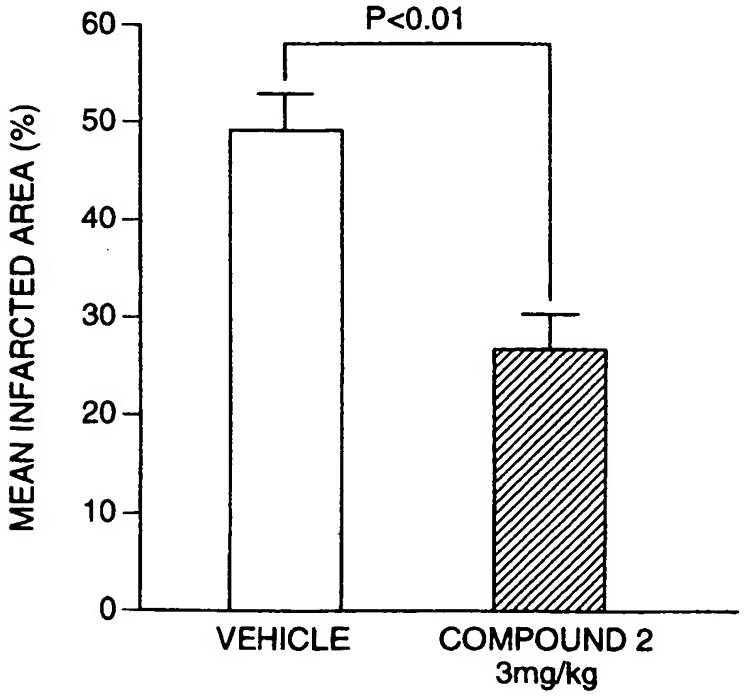


FIG.3

EFFECT OF COMPOUND 3 ON INFARCTED AREA IN TRANSIENT ISCHEMIC RATS

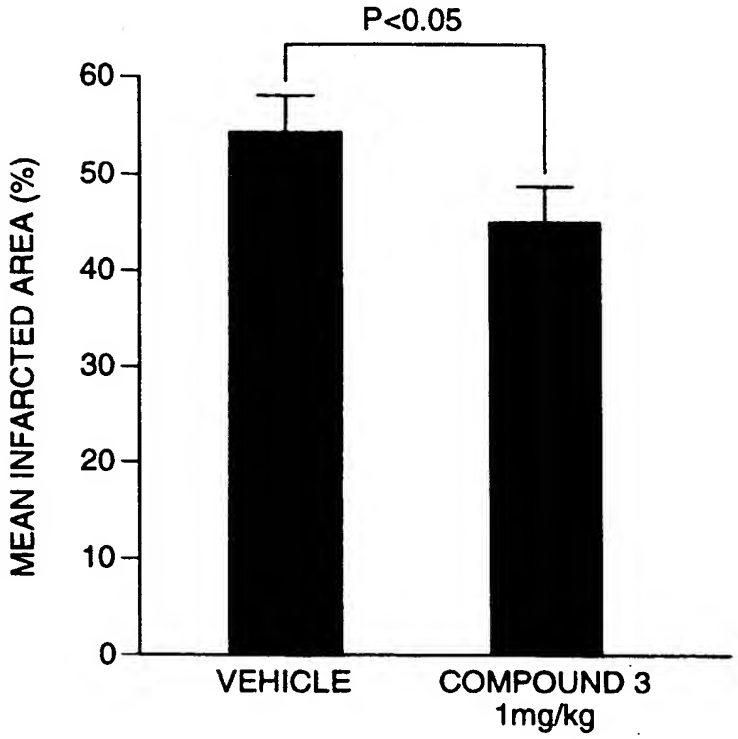


FIG.4

EFFECT OF COMPOUND 1 ON BRAIN EDEMA IN TRANSIENT ISCHEMIC RATS

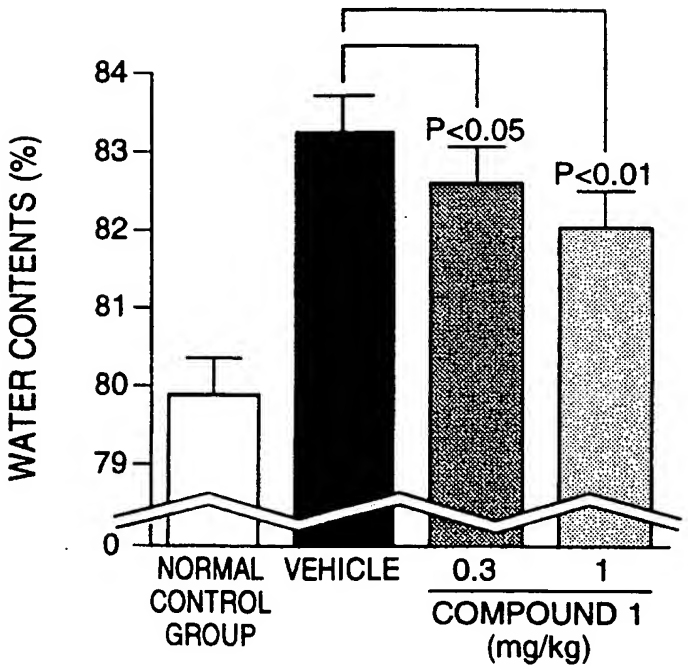


FIG.5

EFFECT OF COMPOUND 2 ON BRAIN EDEMA IN TRANSIENT ISCHEMIC RATS

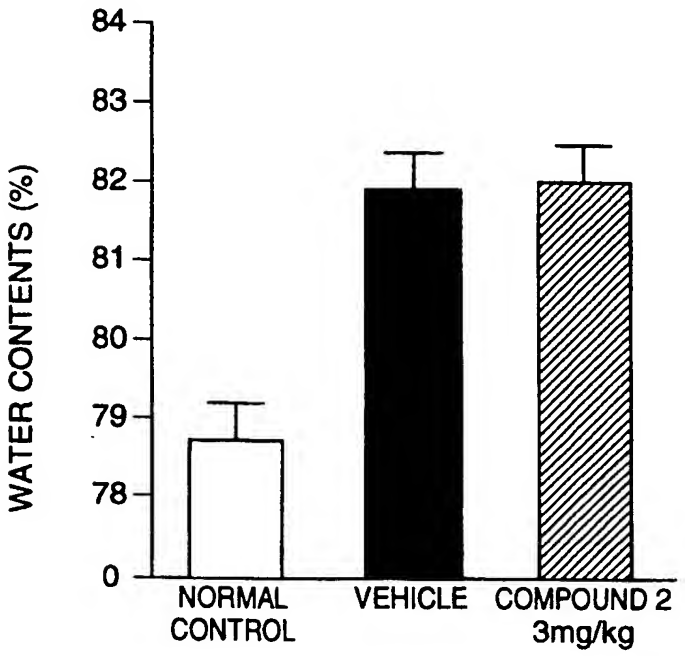
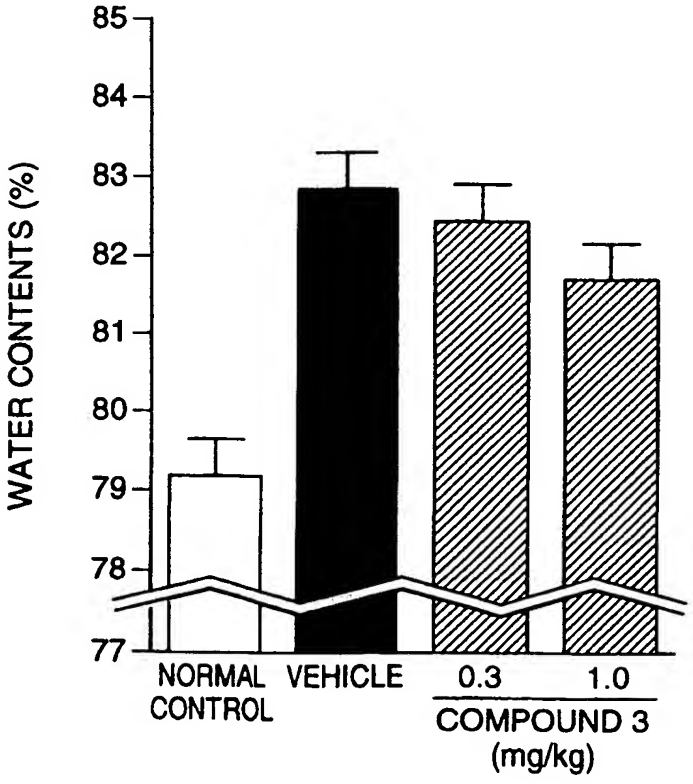


FIG.6

EFFECT OF COMPOUND 3 ON BRAIN EDEMA IN TRANSIENT ISCHEMIC RATS



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(54) Pharmaceutical compositions for the treatment of ischemic brain damage

(57) The use of a compound which has Na^+/H^+ exchange system inhibition activity, in particular a substituted guanidine derivative, or a pharmaceutically acceptable acid addition salt thereof, in the manufacture of a pharmaceutical composition for the treatment of ischemic brain damage such as cerebral infarction, cerebral embolism and cerebral thrombus.

EP 0 937 459 A3

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 99 30 0678

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP 0 787 728 A (SUMITOMO PHARMA) 6 August 1997 (1997-08-06) * abstract * * page 4, line 5 - line 7 * * page 4, line 23 - line 24 * * table 1 * * examples 44,241 * * claims 1-16 *	1-4,6-9	A61K31/40 A61P9/10
D,X	EP 0 708 091 A (SUMITOMO PHARMA) 24 April 1996 (1996-04-24) * abstract * * page 2, line 19 - line 29 * * page 12, line 13 * * page 91, line 37 - page 92, line 33 * * claims 1-27 *	1-3,5-9	
X	EP 0 639 573 A (HOECHST AG) 22 February 1995 (1995-02-22) * abstract * * page 5, line 33 * * page 6, line 24-27 * * page 6, line 33 - line 36 * * examples 41,104 * * page 30, line 1 - line 19 * * claims 1-19 *	1-4,6-9	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K
X	EP 0 622 356 A (SUMITOMO PHARMA) 2 November 1994 (1994-11-02) * abstract * * page 10, lines 2 and 12 * * page 12, line 6 - line 15 * * table 1, entry 1 * * table 2, examples 1 and 9 * * claims 1-15 *	1-4,6-9	

~~The present search report has been drawn up for all claims~~

Place of search	Date of completion of the search	Examiner
MUNICH	15 March 2000	Taylor, G

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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EPO FORM 1503 03.82 (P04C01)

European Patent Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 99 30 0678

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1-4 (part), 6-9 (part)

   The use of compounds having formula (a).

2. Claims: 1-3 (part), 5-9 (part)

   The use of compounds having formula (b).

3. Claims: 1-3 (part), 7-9 (part)

   The use of compounds having formula (c).

4. Claims: 1-3 (part), 7-9 (part)

   The use of compounds having formula (d).

5. Claims: 1-3 (part), 7-9 (part)

   The use of compounds having formula (e).

6. Claims: 1-3 (part), 7-9 (part)

   The use of compounds having formula (f).

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 99 30 0678

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